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A SURVEY OF NOVEL AND USEFUL REACTIONS DISCOVERED THROUGH RESEARCH ON PROSTAGLANDINS

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INTRODUCTION

The prostaglandins, a group of natural products occurring in animal tissues, have attracted widespread attention over the past decade because of their varied and potent biological properties and potential clinical application in a number of therapeutic areas. When the structure of the prostaglandins was elucidated in the early 1960s, organic chemists were immediately presented with the challenge of devising effective total syntheses which would afford adequate quantities of these substances, then available only in small amounts by biosynthetic procedures. This objective received a powerful stimulus from the pharmaceutical industry and as a result, many programmes of synthetic work were initiated in both industrial and academic laboratories.

The consequence has been a flood of publications—to date over 400 in number—which describe the many and varied syntheses now achieved in this area. Although, compared to some classes of natural products, prostaglandins are relatively simple molecules, the assembly of these structures, which have a number of chemically reactive groupings and several chiral centres, placed considerable demands on the resources of organic chemistry, especially as it was desirable that the syntheses should be as short and efficient as possible to satisfy industrial needs. Efforts to meet these requirements led to the discovery and development of new and improved reactions permitting synthetic sequences which would have been difficult or impossible to carry out using existing procedures.

The object of this report is to review these new methods, many of which are of potential value in other areas of synthesis and are likely to be of general interest and utility to organic chemists. An attempt is made to indicate how the reactions discussed arose in the prostaglandin context but it is not the intention of the article to give a complete account of the prostaglandin syntheses themselves, for which the reader is referred to books and other reviews on prostaglandin chemistry.[1–10] In selecting material for inclusion, it was not always possible to distinguish between discoveries falling strictly within the scope of the title, i.e. those brought about directly as a result of prostaglandin research, and work which had arisen in the investigators' laboratory for other reasons but had subsequently found a prostaglandin application. In such cases of doubt the work has generally been included and some reactions have also been mentioned which, although clearly having arisen outside the prostaglandin area, have been extensively used and consequently critically assessed by prostaglandin chemists.

A brief account of prostaglandin structure and nomenclature necessary for an understanding of the material presented is summarised in the figure. Prostaglandins (PGs) may be regarded as derivatives of the basic structure prostanoic acid, which is numbered as shown. The naturally occurring members of the series fall into nine basic groups according to the substitution pattern on the cyclopentane ring, designated by the letters A–I. Individual members of each group are distinguished by the number of double bonds in the side chains which are denoted by the subscript numerals 1, 2 or 3. The three side chain double bond arrangements, which are the same in each group†, are shown in the figure for the E series, the other groups being illustrated by the "2" compounds only. With the F series a further subscript "α" is added to define the stereochemistry of the C_9 hydroxy group. The most recently

†Although in some instances all theoretically possible compounds have not been isolated.

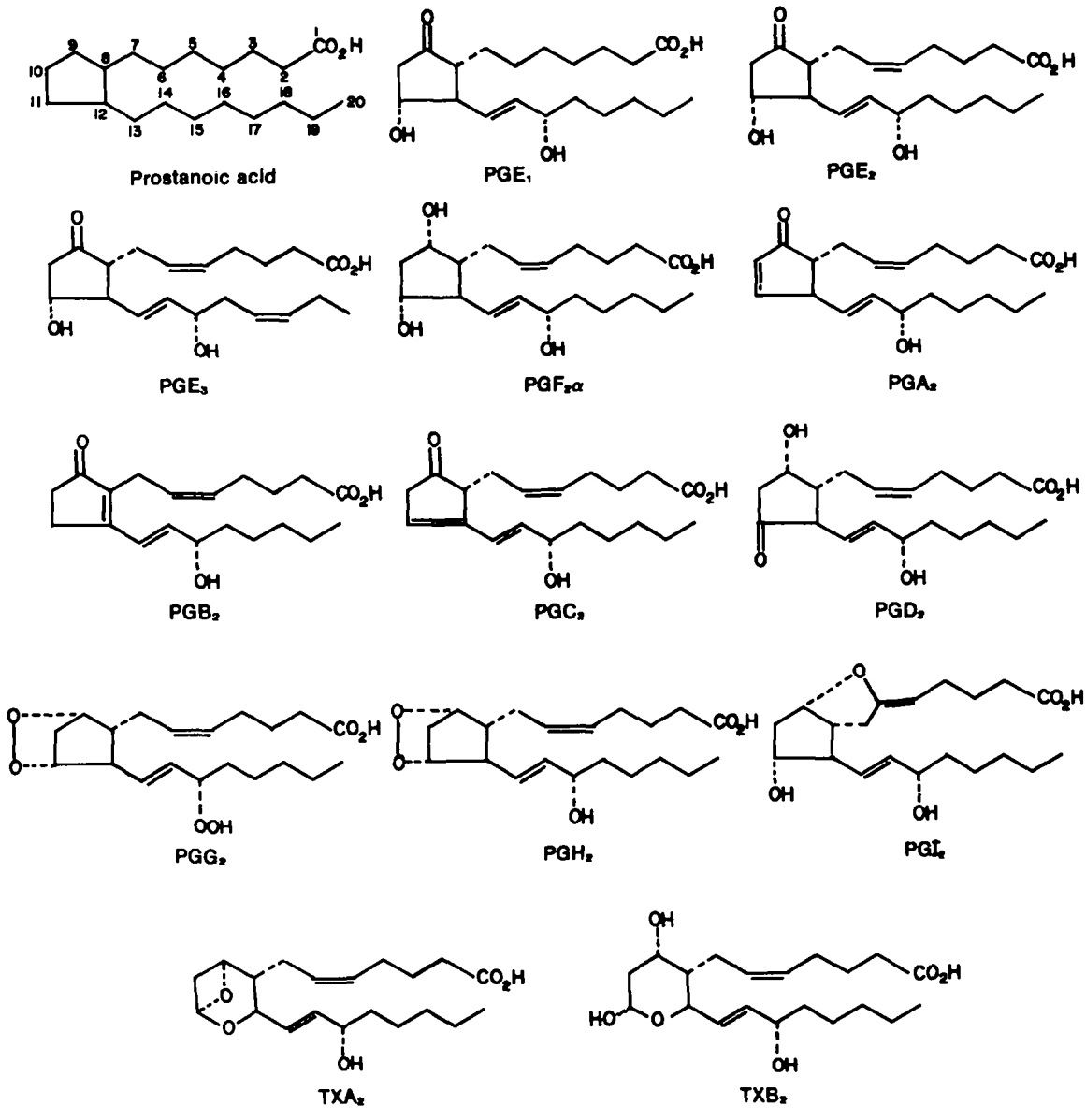


Fig. 1. Prostaglandins and thromboxanes—structure and nomenclature.

discovered prostaglandin, prostaglandin I_2 (PGI_2) has been named and become widely known as prostacyclin.

The structures of the related thromboxanes, TXA_2 and TXB_2 are also shown in the figure.

For convenience throughout this article the prostanoic acid numbering is also used in certain prostaglandin intermediates, even though the complete carbon skeleton is not always present. Also in prostaglandins and appropriate intermediates, the carboxyhexyl side chain is referred to as the α-chain and the hydroxyoctenyl chain as the ω-chain.

The material discussed falls conveniently under three main headings

1. *Methods for preparation of functional groups*
   (a) Oxidation of primary amines to ketones under mild conditions.
   (b) Dehydration of β-hydroxycarbonyl compounds to enones under mild neutral conditions.
   (c) Catalytic dehalogenation via trialkyltin hydrides.
   (d) Olefin formation by novel eliminations of iodohydrins.
   (e) An improved catalytic osmium tetroxide oxidation of olefins to *cis*-1,2-glycols using tertiary amine oxides.

(f) Synthesis of allylic alcohols by nucleophilic vinylation.
(g) Synthesis of α,β-unsaturated aldehydes using 1,3-bis(methylthio) allyllithium.
(h) Oxidation of alcohols to carbonyl compounds under mild conditions.
(i) Reduction of α,β-unsaturated ketones to allylic alcohols.

2. *Chemistry of 2-alkylcyclopentenones*
(a) 2-Alkylcyclopent-2-enones.
(b) 2,3-Disubstituted cyclopent-2-enones.
(c) 2-Alkyl-4-hydroxycyclopent-2-enones.
(d) 2-Alkyl-5-hydroxycyclopent-2-enones.

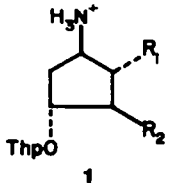
3. *Stereoselective generation of chiral centres*
(a) Stereoselective generation and regioselective cleavage of cyclopentane epoxides.
(b) Conjugate addition of organometallic complexes to cyclopentenones.
(c) Solvolysis of cyclopropyl cations.
(d) Construction and cleavage of internally protected cyclohexanes.
(e) Cleavage of Diels–Alder adducts.
(f) Regiospecific addition of formaldehyde to a cyclopentone by a Prins reaction.
(g) Stereocontrolled cross coupling of a vinylic copper reagent with an allylic electrophile.
(h) Cleavage of hydrindenes.
(i) Synthesis via carbopalladation.
(j) Cleavage of a bicyclo [3.2.0] heptane prepared by a mixed photoaddition of two unsaturated ketones.
(k) Cyclopentane formation by novel intramolecular cyclisations.
(l) Stereoselective reduction of α,β-unsaturated ketones.
(m) Nucleophilic inversion of hydroxyl groups at asymmetric centres.
(n) Stereoselective formation of an epoxide using a controller group.
(o) Constructions of the unstable enol ether system of prostacylin (PGI) under mild conditions.

In Section 1 some new and improved methods are highlighted for the preparation of certain well known functional groups which are of obvious practical importance to organic chemists generally. A complete section (Section 2) has been devoted to 2-alkylcyclopentenones because of the considerable volume of new material which has been contributed to their chemistry by prostaglandin research. Apart from its potential importance in other areas of chemistry based on the cyclopentenone system, e.g. jasmones, some of this work may be suitable for extension to similar transformations in other cycloalkenones and in the steroids. Section 3, the longest part of the Report, is an account of the many stereoselective reactions which have emerged from research on prostaglandins. Although many of the techniques described here have clearly been tailor-made to meet specific requirements, they are potentially adaptable to use in other areas of synthesis and the principles involved offer much scope for imaginative extension and development.

(1) METHODS FOR PREPARATION OF FUNCTIONAL GROUPS

(a) *Oxidation of primary amines to ketones under mild conditions*

In the first prostaglandin syntheses[11,12] by Corey *et al.* at Harvard University, the sensitive β-ketol system 2 of the E prostaglandins was arrived at via an oxidative hydrolysis of an α,γ-amino alcohol derivative 1. This amine to ketone transformation was first accomplished using the Ruschig process, i.e. by preparing the N-bromo derivative of 1 which was subjected to base catalysed dehydrobromination and



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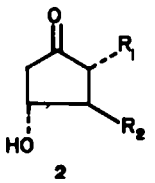

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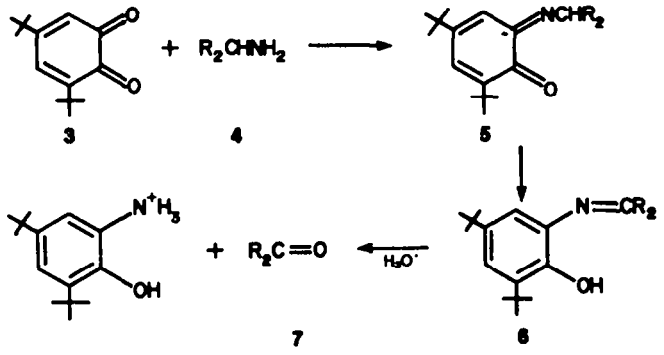
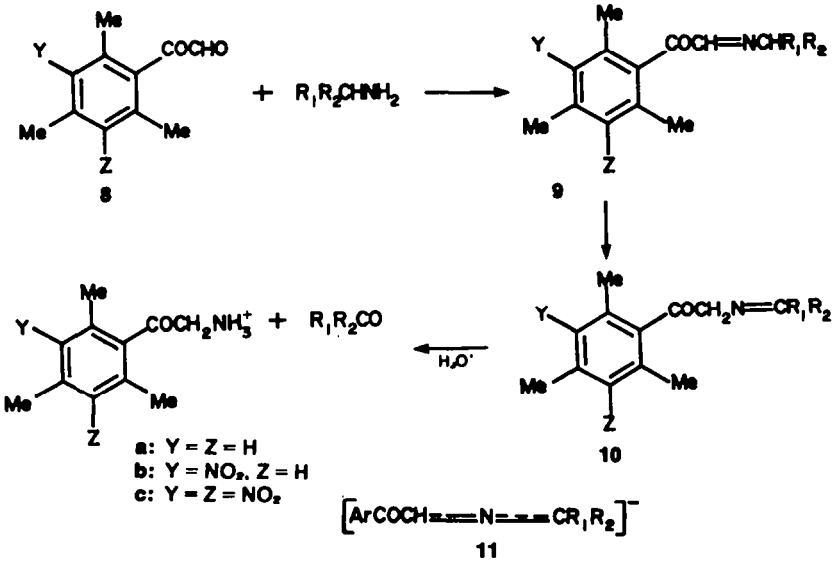
hydrolysis of the resulting imine. However, since it was not certain that this method would be sufficiently gentle for use in this context, Corey and Achiwa[13] developed a new procedure for effecting the primary amine to ketone conversion under extremely mild conditions.

In this new method the appropriate amine **4** was converted to a suitable Schiff base, e.g. **5**, which was rapidly transformed by prototropic rearrangement to an isomeric Schiff base **6**, the latter then affording the desired ketone **7** by hydrolysis in weakly acidic solution.



The key to this reaction lies in the choice of reagent used to form the Schiff base, the principle being that the reagent should possess a reactive carbonyl group to which is attached one or two powerfully π-electron-withdrawing groups, themselves being protected against nucleophilic attack. Also the anion produced by deprotonation of the first Schiff base **5** clearly must be able to assume the optimum geometry for electron delocalization. The readily available 3,5-di-*t*-butyl-1,2-benzoquinone **3** was found to be an extremely effective reagent for this purpose, the substitution pattern being such as to obstruct nucleophilic approach by an amino group to all but C_1 of the aromatic ring, thus favouring formation of **5**. It would be expected that deprotonation of **5** to form the required intermediate for prototropic rearrangement to **6** would be greatly facilitated because of the stability of the intermediate anion and there is ample difference between the free energies of **5** and **6** to force the conversion thermodynamically. The reaction of the amine **4** and ketone **3** to form Schiffs base **6** was effected in methanol at 23° and ketone **7** was generated from **6** by hydrolysis at pH 2–4 at 23°.

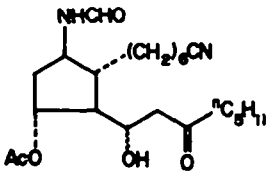
Corey and Achiwa[13] also described a second type of reagent for this purpose, characterised by the presence of the α-ketoaldehyde system in a structure which allows nucleophilic attack only at the formyl group. These reagents—mesitylglyoxal **8a** and its 3-nitro- and 3,5-dinitro-derivatives **8b** and **c**—also rely on the principle of steric shielding to control the site of electrophilic reactivity in the reagent. The electron-withdrawing mesitoyl group strongly facilitates the prototropic rearrangement **9**→**10**—effected at 23° in the presence of a tertiary amine or alkali metal alkoxide—which may be expected to occur via an anion of structure **11**.



The general utility of these methods, which clearly have many potential applications, was shown by a number of examples; yields were usually high.

(b) *Dehydration of β-hydroxycarbonyl compounds to enones under mild neutral conditions*

In Corey's early prostaglandin synthesis[11] a method was required for dehydration of the β-hydroxyketone 12 to the enone system 13 under conditions mild enough to avoid accompanying elimination of the 11-acetoxy group. It was found that this could be accomplished using dicyclohexylcarbodi-imide in ether with cupric chloride as catalyst.



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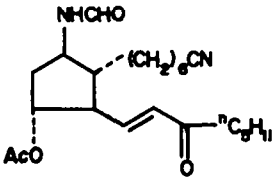

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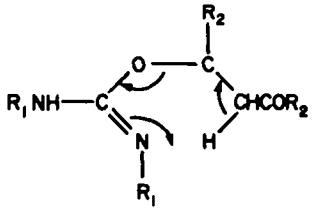
The method was devised on the expectation that reaction of the β-hydroxy function with carbodi-imide would lead to a carbamidate derivative which should be susceptible to cycloelimination of the form 14.



14

This represents a new method for the dehydration of β-hydroxycarbonyl compounds under mild non-acidic, non-basic conditions and has been shown to be of broad generality.

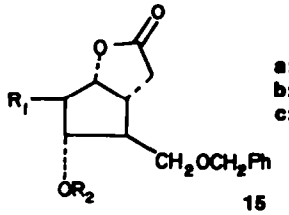
(c) *Catalytic dehalogenation via trialkyltin hydrides*

In Corey's second basic approach to prostaglandin synthesis the iodolactone **15a** was deiodinated with trialkyltin hydrides to the intermediate **15b**, a precursor of the E and F prostaglandins. In connection with this work a procedure was developed in which the tin hydride was used in catalytic rather than in stoichiometric amounts, since in the latter case the product had to be separated from a full one equivalent of trialkyltin halide which limited the method's usefulness.[14] In the new procedure the organic halide R^1X and 0.1–0.3 equivalents of trialkyltin chloride in ethanol was treated with sodium borohydride in ethanol which led to the *in situ* generation of the tin hydride and subsequent dehalogenation according to the following cycle:

$$2R_3SnX + 2NaBH_4 \longrightarrow 2R_3SnH + 2NaCl + B_2H_6 \quad (1)$$

$$R_3SnH + R^1X \longrightarrow R_3SnX + R^1H. \quad (2)$$

In most experiments the reaction was carried out in Pyrex with irradiation by a 100-W mercury floodlamp so that reaction occurred rapidly at or below room temperature. Ethanol was used as the solvent in order to trap the resulting diborane. This dehalogenation procedure, which did not interfere with the ester and lactone functions functions elsewhere in the molecule, was illustrated with several different organic halides R^1X; yields were high.

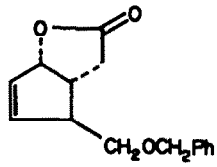


15

a: $R_1 = I$, $R_2 = Ac$
b: $R_1 = H$, $R_2 = Ac$
c: $R_1 = I$, $R_2 = H$

(d) *Olefin formation by novel eliminations of iodohydrins*

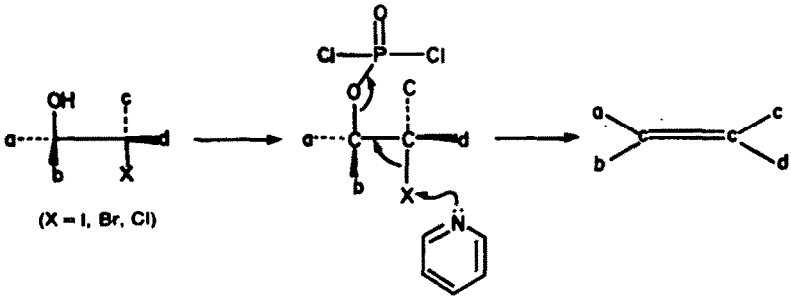
Two methods have been devised for the elimination of iodohydrins to olefins with high efficiency under mild conditions, the need for which arose in the transformation of intermediate **15** to the cyclopentene **16**, required for the synthesis of prostaglandins of the A series and of 11-deoxyprostaglandins.



16

In the first of these methods, by Corey and Grieco,[15] the elimination was achieved in >99% yield using methanesulphonyl chloride in pyridine at 0–20°.

Crabbé and Guzmán[16] effected the same transformation by reacting intermediate **15c** with freshly distilled phosphorus oxychloride in pyridine at 0°—room temperature. The generality of this procedure, the mechanism of which may be represented as shown **17**, was subsequently demonstrated with other examples.[17]



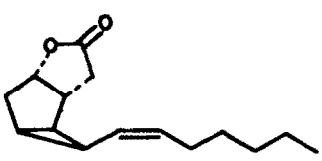
17

Both of these methods have the advantage that they avoid the use of a reducing agent, e.g. zinc or stannous chloride, normally used in this reaction.

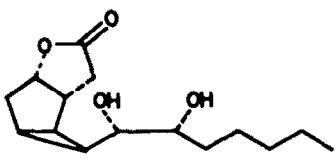
(e) *An improved catalytic osmium tetroxide oxidation of olefins to* cis-1,2-*glycols using tertiary amine oxides*

Although osmium tetroxide is a very effective reagent for the oxidation of olefins to *cis*-1,2-glycols, its high cost and toxicity, coupled with cumbersome work-up procedures, are a disincentive to its use, particularly on a large scale. These problems have been diminished by employing osmium tetroxide in catalytic, rather than in stoichiometric amounts, regenerating it with another oxidant which has been provided by chlorate or hydrogen peroxide.

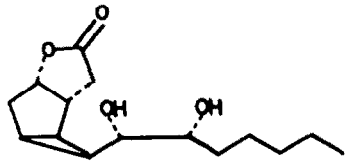
However catalytic osmylation with these oxidants was found to give rise to some further oxidation of the diol to an α-ketol, resulting in yield losses and separation problems. Upjohn workers, when investigating the oxidation of the prostaglandin intermediate **18** to the *cis*-glycols **19a** and **19b**, discovered an improved catalytic osmylation procedure using N-methylmorpholine-N-oxide (NMO) as the second oxidant with which this side reaction did not occur.[18] Their reaction, which afforded glycols **19a,b** in >95% yield, was carried out in aqueous acetone at room temperature using 0.2–1.0 mole% of osmium tetroxide and one mole of the amine N-oxide, followed by a simple work-up procedure involving reduction of the osmium tetroxide with sodium hydrosulphite and its adsorption on magnesium silicate and then acid extraction of the amine.



18



19a

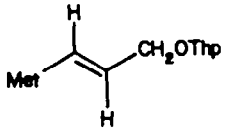


19b

The generality of this reaction and its greater efficiency compared to other *cis*-glycolisation procedures has been illustrated for a variety of differently functionalised olefins. It was found that other simple aliphatic amine oxides can also be used in this reaction, but NMO was preferred because it generally gives a faster reaction rate and can be easily prepared.

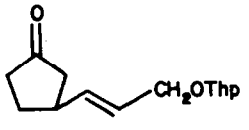
(f) *Synthesis of allylic alcohols by nucleophilic vinylation*

Corey and Wollenberg[19] have reported that *trans*-1-tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether **20a**, prepared in one step from bis(tri-*n*-butyltin)oxide and propargyl tetrahydropyranyl ether, can be used via the vinylic nucleophiles **20b,c** to effect the nucleophilic introduction of the *trans*-CH=CHCH$_2$OH unit. Thus **20a** was treated with *n*-butyllithium in THF to give the lithium reagent **20b** and then with 1-pentynylcopper to form the mixed Gilman reagent **20c** which underwent conjugate addition (at −78 to 50°) to 2-cyclopent-2-enone affording the vinyl alcohol derivative **21** in 80% yield.



20

a: Met = *n*-Bu$_3$Sn
b: Met = Li
c: Met = Cu—C≡CC$_3$H$_7$



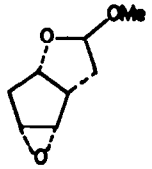
21

Examples are given of similarly high yields with other cycloalkenones. It was also shown that **21b** can be used for the extension of chains by reaction with an alkyl halide; thus reaction with 1,8-dibromoacetone gave the bis vinyl alcohol derivative **22** in 85% yield. These reagents are clearly of great potential value for the introduction of the *trans* allylic alcohol group to a wide variety of molecules.

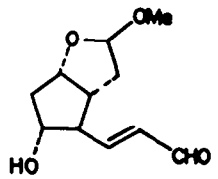
22

(g) *Synthesis of α,β-unsaturated aldehydes using 1,3-bis(methylthio)allyllithium*

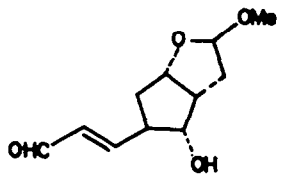
Corey and Noyori[20] found that the epoxide **23** could be elaborated to an isomeric mixture of unsaturated aldehydes **24a,b** using 1,3-bis(methylthio)allyllithium **25**. The latter, a new reagent easily prepared by reaction of epichlorhydrin and sodium methylthiolate to **26a**, methylation to **26b** and then treatment with lithium di-isopropylamide in THF, functions as a synthetic equivalent of the unknown and probably intrinsically unstable anion **25**. The reaction of **25** with epoxide **23** was carried out in THF at −78° under argon to give a mixture of the isomeric products **28a** and **28b**, which was hydrolysed with mercuric chloride-calcium carbonate in aqueous acetonitrile under argon at 50° to give aldehydes **24a** (30% yield) and **24b** (40% yield).



23

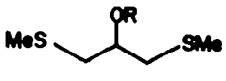


24a



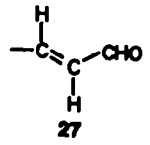
24b

25



26

a: R = H
b: R = Me



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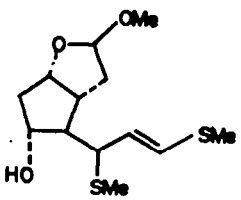
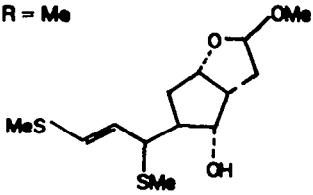


28a

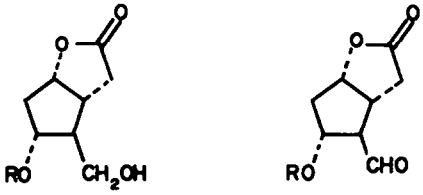


28b

Reagent 25 has also been shown to shown to undergo a similar reaction with other epoxides as well as with alkyl halides and carbonyl compounds.[21] This is clearly a valuable new approach to the synthesis of conjugated aldehydes with many potential applications.

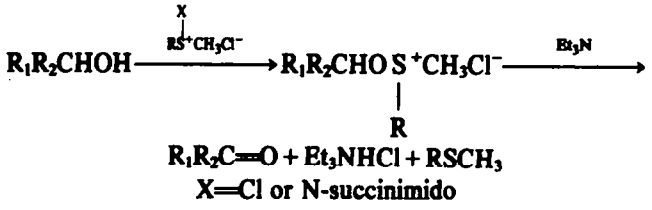
(h) *Oxidation of alcohols to carbonyl compounds under mild conditions*

Aldehyde intermediates, from which the prostaglandin side chains are elaborated via suitable Wittig reactions, are commonly encountered in prostaglandin chemistry. It has often been necessary to generate these aldehydes under mild, non-acidic conditions so as not to interfere with other groupings in the molecule, for example an acid sensitive THP-ether. This problem was encountered in the well-known approach to prostaglandins by Corey in which the lactone ester aldehyde 30 was prepared by oxidation of the corresponding alcohol 29.[22-23]

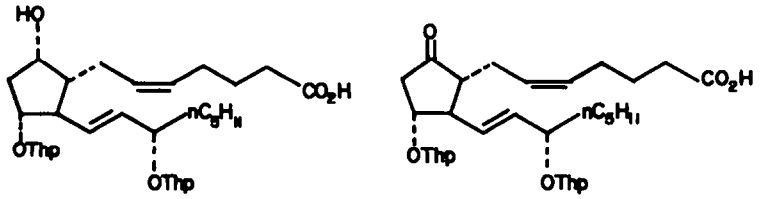


29 R = $COCH_3$, *p*PhPhCO 30

This oxidation was originally carried out using the modified form of the chromium trioxide complex due to Collins, Hess and Frank (Collins reagent)[23] which has been used extensively in similar oxidations in other prostaglandin syntheses. However this method, although effecting the transformation of 29 to 30 in high yield (90%), suffered from the disadvantage of being difficult to carry out on a multimolar or even molar scale. Also, in the author's experience, this reagent can give rise to difficulties in preparation in which the hygroscopic nature and flammability of the pyridine-chromium trioxide can be troublesome. More recently Corey and Kim have developed a new reagent based on complexes of a sulphide, e.g. methyl sulphide, with chlorine or N-chlorosuccinimide, which has been shown to be a highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds.[24,25] This process may be summarised as follows:



This method was used for the oxidation of 29 to 30 using the reagent in which X is N-succinimide in toluene-methylene chloride. However, it was found that the aldehyde product 30 was contaminated with variable amounts of starting alcohol 29, even when an excess of oxidising agent was employed, possibly because of the insolubility of the sulphoxonium intermediate. Much better results were obtained using as the reagent the 1:1-complex of chlorine with methyl phenyl sulphide in carbon tetrachloride and methylene chloride mixture, (90% yield). The methyl sulphide-N-chlorosuccinimide reagent gave very good results in the oxidation of the potentially labile hydroxy acid 31 to the keto acid 32, the penultimate stage in a synthesis of PGE_2. Corey and Kim have also used a dimethyl sulphoxide-chlorine complex for alcohol to carbonyl conversion.[26] Weinshenker and Shen[27] successfully oxidised 29 to 30 using a modified Moffatt oxidation in which a carbodi-imide is linked to a crosslinked polymer matrix. This reagent was used to oxidise a range of alcohols to aldehydes and ketones and was found to be particularly useful in dealing with highly sensitive compounds.



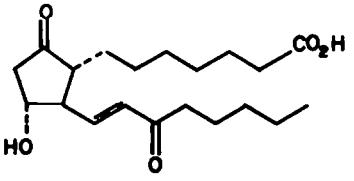
31 32

Other methods for effecting the oxidation of alcohols to carbonyl compounds which have been reported in recent years include an improved version of the chromiumtrioxide complex[28] in which the complex was generated and used in methylene chloride solution directly, thus avoiding the difficulties encountered when it is isolated in the solid form. Reagents derived from chromyl chloride,[29] chromium trioxide in hexamethylphosphoric triamide[30] and pyridinium chlorochromate[31] have also been used. The last method, which is recommended for moderate to large scale oxidations, has been found particularly useful in the author's laboratory for oxidations of alcohols to aldehydes in prostaglandin-type intermediates, because of its commercial availability, safety, stability on storage and simplicity of use. Although development of these new methods has obviously also been influenced by wider considerations, the needs of prostaglandin chemists have clearly provided an incentive for research in this area and the limited methodology available at the outset of prostaglandin work has now expanded into a variety of different methods from which, for any particular requirement, a choice can be made.

(i) *Reduction of α,β-unsaturated ketones to allylic alcohols*

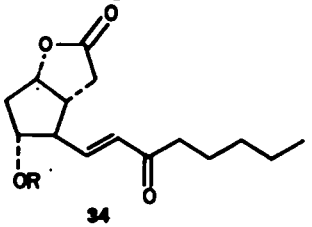
Many prostaglandin syntheses include a step in which an α,β-unsaturated ketone is reduced to form the allylic alcohol system of the ω-chain. In the early prostaglandin work this was carried out using zinc borohydride or an alkali metal borohydride, but the regioselectivity of the reaction left much to be desired and a substantial degree of olefin reduction occurred, although this problem can be minimised by working at low temperature.

In subsequent work improved procedures for this reaction have been reported. Thus Miyano, Dorn and Mueller,[32] when reducing the enone 33, found that good results, with only a small amount of olefin reduction, could be obtained using potassium borohydride in a citrate buffer at pH 8. This method, however, which has also been used successfully by the author in the 11-deoxyprostaglandin series,[33] involves large reaction volumes and difficult work up procedures which can be a disadvantage for use on a large scale.



33

Corey *et al.*[34] successfully used a reagent prepared from optically active di-isopinocamphenylborane and methyl lithium in the presence of a Lewis base (hexamethylphosphoramide) (at 97°–100°) for reduction of the enone 34 to the allylic alcohol, with only 2.8% of the 13,14-dihydro product. This approach was also designed with the object of achieving stereoselectivity and is discussed more fully in Section 3 of this Report.

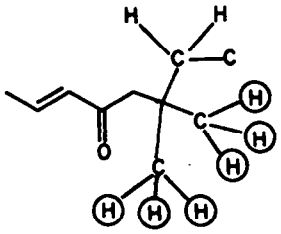


34

R = *p*-phenylbenzoyl

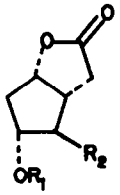
More recently, the readily available lithium tri-*s*-butylborohydride (L-Selectride)[35,36] has been used very successfully for reactions of this type and is recommended because it is simple to use and highly regioselective. However, Picker, Anderson and Leovey[37] have shown that when K-Selectride was used for reduction of the 17,17-dimethyl-substituted compound **36a**, the main products were the deoxy-olefin **36b** (31%) and the saturated ketone **36c** (60%), with minor amounts (9%) of a mixture of alcohols (**36d–e**) which was shown by NMR to be largely saturated.

This complete change in the regioselectivity of the reaction may be attributed, on steric grounds, to the operation of Newman's rule of six, since the gem dimethyl groups introduce six additional atoms (encircled in the diagram, **35**) in position 6 relative to attack at the carbonyl.



35

It was found, however, that the desired reduction of ketone **36a** to the allylic alcohols **36d** could be effected without conjugate reduction, with aluminium isopropoxide in the classical Meerwein–Pondorf–Verley reaction, a method which had, interestingly, been reported earlier by Raphael and ICI workers[38] as being particularly successful for reduction of enones such as **34**.



36

R_1 = *p*-phenylbenzoyl

	R_2
36a:	$CH{=}CH\,CO\,CH_2CMe_2Pr$
b:	$CH_2CH{=}CHCH_2CMe_2Pr$
c:	$CH_2CH_2COCH_2CMe_2Pr$
d:	$CH{=}CHCHOHCH_2CMe_2Pr$
e:	$CH_2CH_2CHOHCH_2CMe_2Pr$

Nevertheless it has been shown [39] that in the case of a cyclic 2-en-1,4-dione, use of the aluminium isopropoxide method and most metal hydrides were unsatisfactory and here, and with cyclic-2-enones, di-isobutylaluminium hydride was recommended as being the reagent of choice.

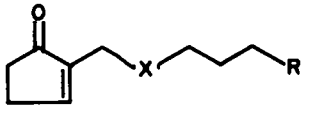
This is clearly another area in which no single reagent stands out as being necessarily the best method for use in every case, and prostaglandin research has undoubtedly played a useful part in assessing the advantages and limitations of the several useful methods now available.

(2) CHEMISTRY OF 2-ALKYLCYCLOPENTENONES

2-Alkylcyclopent-2-enones have been used very extensively as intermediates in prostaglandin synthesis since they readily afford the prostanoic acid skeleton via conjugate addition reactions. The need to achieve efficient routes to the required cyclopent-2-enones led to several new and improved syntheses of this well known class of compounds and to some interesting developments in their chemistry. Some of the earlier work referred to here has also been discussed by Ellison in a general review on the synthesis of cyclopentenones.[40]

(a) 2-*Alkylcyclopent-2-enones*

ω-Substituted 2-alkylcyclopentenones **37** were required for the syntheses of 11-deoxyprostaglandins and a variety of new methods for their synthesis has been described.



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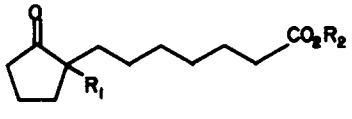


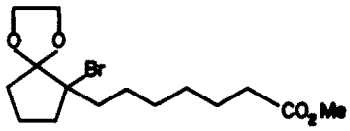
38

a: $R_1 = CO_2Me$, $R_2 = Me$
b: $R_1 = H$, $R_2 = Me$
c: $R_1 = H$, $R_2 = Et$

(i) *Dehydrobromination of bromocyclopentanone derivatives.* Several of the new syntheses are based on adaptations of the classical bromination–dehydrobromination reaction to give conditions which afford satisfactory yields under sufficiently mild conditions.

Ayerst chemists[41] synthesised the enone **37** ($X = CH_2CH_2$, $R = CO_2H$) by bromination of the condensation product **38a** of methyl 2-cyclopentane carboxylate and methyl ω-bromoheptanoate, then effecting both dehydrobromination and decarboxylation in a single step by refluxing with 20% sulphuric acid in ethanol (37% from **38a**). Since methyl 2-cyclopentanone carboxylate is readily available, this two-step process affords a very short route to 2-alkylcyclopent-2-enones from the appropriate alkyl halides.

Later methods were based on bromination of the 2-oxocyclopentanecarboxylate **38b** or its derivatives, prepared, e.g. by decarboxylation of **38a**. Using a procedure described by Garbisch in connection with earlier work on cycloalkenone synthesis, Novák and Szántay[42] reacted enone **38b** with bromine and ethylene glycol to give a mixture of monobromo compounds **39** and **40** (ratio 65:35) in 80% yield, which afforded the enone **37** ($R = CO_2Me$, $X = CH_2CH_2$) (40% yield) on treatment with boiling methanolic sodium hydroxide followed by esterification of the intermediate isomeric unsaturated acids.



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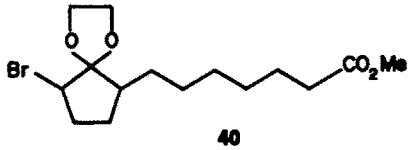
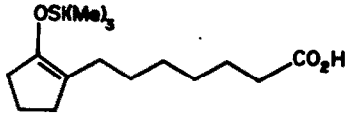


40

Attanasi *et al.*[43] obtained enone **37** ($R = CO_2Et$, $X = CH_2CH_2$) from the 2-alkylcyclopentenone **38c** by bromination with phenyltrimethylammonium perbromide in THF and then dehydrobromination in collidine (52% yield).

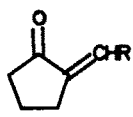
Trost and Kurozumi[44] prepared enone **37**, ($X = CH_2CH_2$, $R = CO_2H$) by bromination and then dehydrobromination (lithium chloride–lithium carbonate) of the trimethyl silyl ether **41**. Crammer, Aizenshtat and Ikan[45] prepared enone **37** ($X = CH_2CH_2$, $R = CO_2Et$) via bromination of the enol acetate of **38c** and dehydrobromination with lithium bromide–lithium carbonate in dimethylformamide (overall yield from **38c**, 47%).



41

There is thus now a variety of satisfactory methods for effecting this bromination–dehydrobromination sequence. The success of this approach is obviously dependent on the fact that the 2-alkylcyclopentenone products are thermodynamically more stable than the corresponding exocyclic compounds. The relative thermodynamic stability of possible alternative products will thus obviously be an important factor in determining where these methods can also be successfully applied to the synthesis of other cycloalkenones.

(ii) *Isomerisation of 2-alkylidenecyclopentanones.* In connection with a May and Baker synthesis of 11-deoxyprostaglandins[33] a method was developed in which 2-alkylidenecyclopentanones **42**, known from earlier work to be readily available by reaction of cyclopentanone morpholine enamine and the appropriate aldehyde, underwent isomerisation to the thermodynamically more stable 2-alkylcyclopentenone **43** on heating at 90–100° with hydrochloric acid in *n*-butanol.[46] This reaction was used for the preparation of the prostaglandin intermediate **37** ($R = CH_2OH$, $X = CH_2CH_2$) and the general utility of the method was subsequently illustrated by its application to a series of unsubstituted 2-alkylcyclopent-2-enones **43** (R = alkyl). Yields for the isomerisation **42** to **43** were 47–74%.



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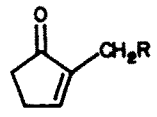
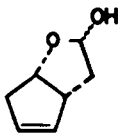


43

Although this isomerisation using acidic conditions had been reported previously, e.g. by heating with polyphosphoric acid, it had not found practical application in cyclopentenone synthesis, probably

because of the variable yields due to competing intermolecular condensation. The new method, however, affords consistently good results and is simple to operate.

(iii) *Isomerisation of cyclopent-3-enones.* Two 2-alkylcyclopent-2-enone intermediates, **37** (X = CH=CH, R=CO_2Me) and **49**, required for the synthesis of "2" type prostaglandins, were synthesised via isomerisation of the corresponding 2-alkylcyclopent-3-enones **46** and **48**.



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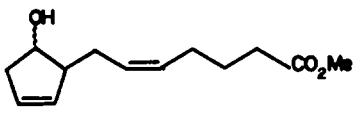

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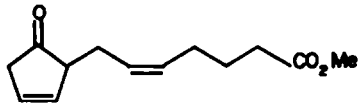

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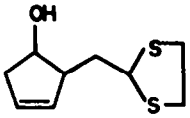

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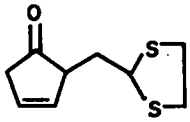

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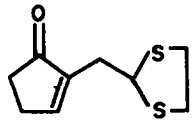


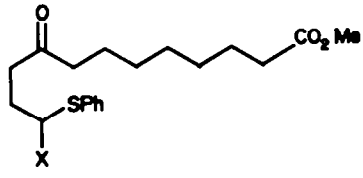
49

The isomerisation of **46**, described by Grieco and Reap,[47] was effected in 85% yield using 1N sodium hydroxide – 95% ethanol at 35–40°, by modification of a procedure which was first described by Grieco[48] in a synthesis of *cis*-jasmone. Isomerisation of **48**, in a synthesis due to Bartman, Beck and Lerch,[49] interestingly took place, simultaneously with oxidation of the alcohol precursor **47**, when the latter was treated with dicyclohexylcarbodi-imide in dimethylsulphoxide at room temperature.

Intermediates **46** and **48** were obtained via Wittig reactions on lactol **44**, to give the unsaturated alcohols **45** and **47**, ketone **46** being prepared by Jones oxidation of alcohol **45**.

Although this approach involves a number of stages it is potentially useful for the synthesis of 2-alkylcyclopent-2-enones containing a double bond in the 2,3-position of the side chain or other groupings in that region, which would be expected to interfere with the operation of methods (i) and (ii).

(iv) *Cyclisation of a γ-ketoaldehyde.* An interesting development of the well known base-catalysed cyclisation of γ-ketoaldehydes was reported by Bakuzis and Bakuzis.[50] These workers constructed a latent aldehyde in the form of a chloroalkylphenyl thioether **50b** which has hydrolysed with cupric oxide–cupric chloride in aqueous acetone and the resulting ketoaldehyde added, in ethanol, to 1% sodium hydroxide at 75° to effect cyclisation (and ester hydrolysis) (in 63% yield) affording cyclopentenone **37** (R = CO_2H, X = CH_2CH_2).

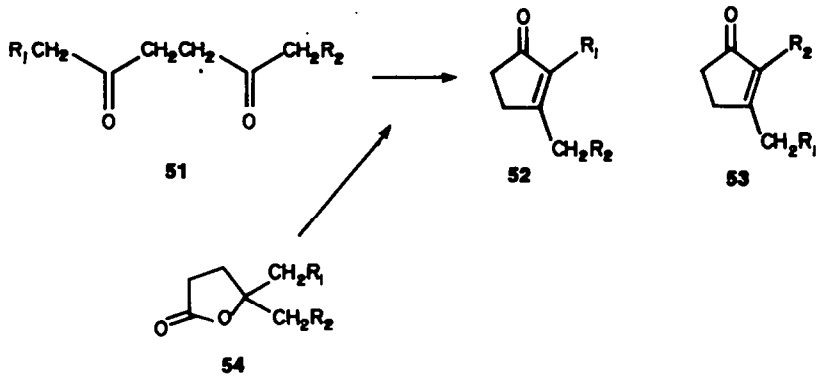


50
a: X = H
b: X = Cl

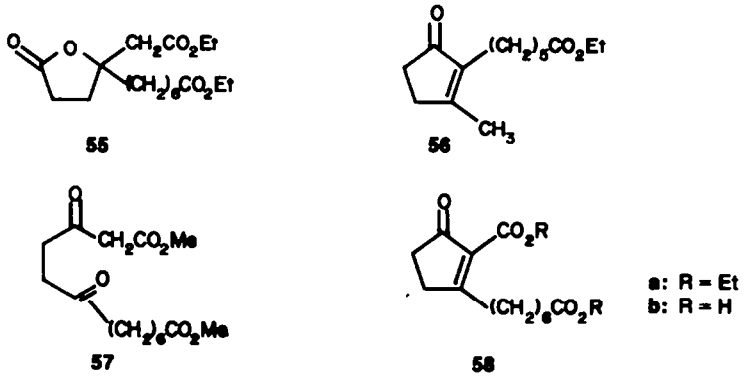
Phenylthioethers of type **50b** are easily prepared by chlorination with N-chlorosuccinimide of the parent thiol **50a**, which is made by reacting the acid chloride-ester of an α,ω-dicarboxylic acid and the Grignard reagent of the appropriate 3-bromoalkylphenyl sulphide. Suitable methods for the synthesis of γ-ketoaldehyde intermediates are relatively few in number and this is clearly a useful new method for generating them in relatively few stages.

(b) 2,3-*Disubstituted cyclopent-2-enones*

Although 2,3-disubstituted cyclopent-1-enones are readily prepared by base-catalysed cyclisation of γ-diketones **51**; except where the diketone is symmetrical **51** ($R_1 = R_2$), or with a monomethyl ketone **52** (R_1 = H), the reaction gives a mixture of the two alternative products **52** and **53** which can be difficult to separate.



A similar situation occurs with the well known polyphosphoric acid rearrangement of γ-lactones **54** to cyclopentenones. These reactions were studied by Finch, Fitt and Hsu[51] in connection with the synthesis of a prostaglandin intermediate when it was found that cyclisation of lactone **55** with polyphosphoric acid gave, with accompanying decarboxylation, a low yield of enone **56** and not the alternative product **58a**.



It was found that the latter, which was in fact the desired product, could be obtained in good yields by cyclisation of the diketone **57**. This cyclisation, which was evident under very mild conditions, was here conveniently carried out, simultaneously with ester hydrolysis, by refluxing in aqueous methanolic potassium carbonate to give the diacid **58b** in 71% yield. These findings afford a useful insight into the directing influence of the ethoxycarbonyl grouping and an effective means of synthesising the enones of type **58** and products which may be derived therefrom.

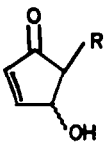
Finch *et al.*[52] also prepared a 2,3-disubstituted cyclopent-2-enone prostaglandin intermediate **60** by bromination of the enol acetate mixture of the corresponding saturated ketone **59** followed by dehydrobromination with triethylamine (yield 68%) but found that direct bromination of **59** and base treatment gave a comparable overall yield (**59**→**60**; 61%).

(c) *2-Alkyl-4-hydroxycyclopent-2-enones*

2-Alkyl-4-hydrocyclopent-2-enones **67** have been used extensively in the synthesis of natural prostaglandins by conjugate addition of organometallic complexes and a number of new methods for their synthesis have been developed, aimed particularly at products with the hydroxyl in the required α-configuration.

Stork, Kowalski and Garcia[53] showed that they can be prepared conveniently by cleavage of the epoxides **62** of the appropriate 2-alkylcyclopent-3-enones which are readily synthesised from cyclo-

pentadiene epoxide. Epoxides of type **62** can *a priori* undergo base-catalysed elimination in two different directions to give either the required enone **63** or its isomer **61**. However, although the desired product **63** is the more stable isomer, the reaction, which was carried out with triethylamine at room temperature, in fact gave a very high yield of **61**, the product of kinetic control. It might be expected that **61** could then be induced to undergo isomerisation to **63** via hydration to the diol **64** followed by dehydration. This could be effected in very good yield with dilute base (1% sodium hydroxide) but results were only reliable with the stereoisomer of **61** in which the hydroxy group and the side chain are in the *cis* relationship, thus leaving one face of the cyclopentenone entirely unhindered and allowing a relatively high rate of hydration. However, it was found that cyclopentenones **61** were these functions are in the *trans* relationships can also be induced to undergo this transformation in high yield if chloral is added with the base treatment. The hydration is then made effectively intramolecular, presumably because the reaction proceeds via the acetal intermediate **65** which then eliminates.



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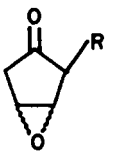

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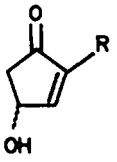

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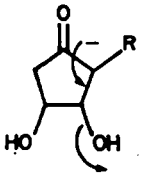

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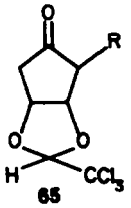
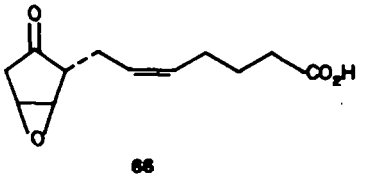


65

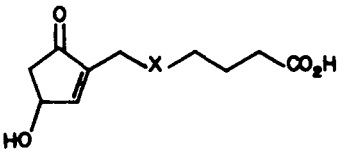
The results of this study were then applied to the transformation of epoxide **66** into prostaglandin intermediate **67** (X = CH=CH) which was effected, without the need to isolate the intermediate hydroxy enone **68**, by treating **66** with base (triethylamine ether–methylene chloride) and then adding anhydrous chloral.

This reaction was also examined by Floyd[54] who showed that epoxide **66** underwent opening in a threefold molar excess of aqueous sodium carbonate at room temperature to give approximately equal amounts of hydroxyenone **67** and the unwanted isomer **68** (X = CH=CH). This epoxide opening was complete in 3 hr, but when the reaction was allowed to proceed for 24 hr, equilibration occurred to a mixture consisting very largely of **67**, with less than 5% of **68** (barely detectable in ^{1}H NMR spectrum).

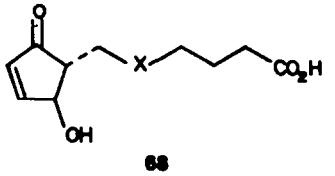
The transformation of hydroxyenones **68** to enones **67** was also studied by Piancatelli and Scettri.[55] These workers found that enone **68** (X = CH_2CH_2, *t*-butyl ester), which they prepared by rearrangement of the furyl carbinol **69**, with polyphosphoric acid in aqueous acetone underwent isomerisation to the *t*-butyl ester of **67** (X = CH_2CH_2), in 95% yield, by adsorption on alumina and elution with benzene–ether.



66



67



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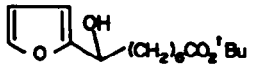
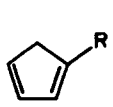


69

It was suggested that this interesting transformation might proceed via a dehydration-hydration sequence involving heterogeneous catalysis, with initial formation of an unstable cyclopentadienone which immediately changes into the more stable α,β-unsaturated ketone **67**. This assumption is supported by the fact that when the C=C double bond of **67** is reduced, only the dehydration reaction occurs with initial formation of the more stable α,β-unsaturated ketone.

In fact, by catalytic reduction of $Pd/CaCO_3$ in methanol followed by elution of alumina (Brockmann grade III basic) with benzene, **68** (*t*-butyl ester) underwent dehydration to enone **37** ($X = CH_2CH_2$, $R = CO_2{}^tBu$) in nearly quantitative yield.

Sih *et al.*[56] investigated the synthesis of 4-hydroxycyclopentenones from cyclopentadiene **70**. The latter when subjected to a 1,4-cycloaddition with chemically generated singlet oxygen (from sodium hypochlorite and hydrogen peroxide in ethanol at −10°) gave a 20–40% yield (the yield increased to 55% if the methyl ester was used, the isomer ratio remaining unchanged) of a 1:4 mixture of enones **63** and **71** ($R = (CH_2)_6CO_2Et$), which were readily separated by column chromatography. When the mixture was oxidised with Jones reagent to the diketone **72** and then reduced back to the hydroxyenones, it was found that the ratio of products **63**:**71** obtained depended upon the reducing agent employed, being 1:9 with lithium tri-*tert*-butoxyaluminium hydride and 2:1 when aluminium isopropoxide was employed.



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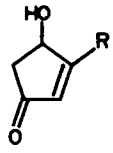

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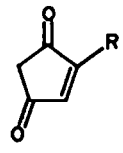
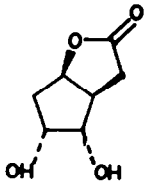


72

$R = (CH_2)_6CO_2Et$

A group at the Hungarian Academy of Sciences[57] described a highly stereoselective route to the required optically active (α)-epimer of hydroxyenone **67** in which the diol **73** was prepared via osmium tetroxide-sodium chlorate dihydroxylation of the corresponding olefin intermediate (80–92% yield), the α-configuration of the oxygen functions arising from the directing influence of the lactone ring. The diol **73** was then taken forward to the acetonide **74** from which the hydroxycyclopentenone **67** (X = CH=CH) arose (in 83% yield) on careful hydrolysis in 20% sulphuric acid at 0°, followed by dehydration with oxalic acid and sodium oxalate at room temperature.



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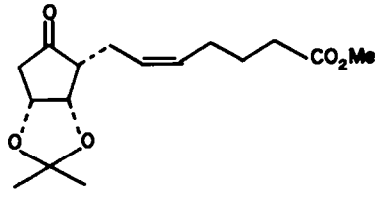
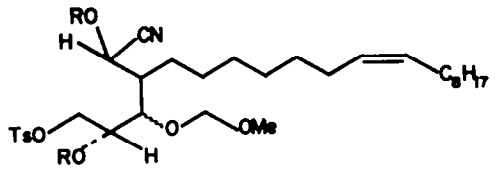


74

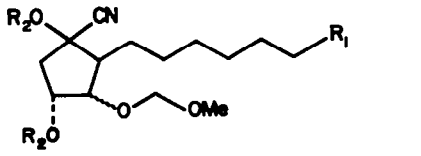
Two interesting new cyclisation methods for the formation of 2-alkyl-4-hydroxycyclopent-2-enones have been reported. Stork and Takahashi[58] synthesised enone **67** via cyclisation, with sodium hexamethyldisilazane in refluxing benzene, of the cyanohydrin **75** (85% yield), the latter having been constructed from isopropylidene-D-glyceraldehyde. The cyclisation product **76a** afforded, via the sequence-olefin cleavage, hydrolysis of ethoxyethyl and esterification—the cyanohydrin ester **76b** which underwent elimination **67** (α-OH epimer, $X = CH_2CH_2$, methyl ester) in 80% yield on treatment with 2% sodium hydroxide in ether—THF at 0°, followed by acidification with hydrochloric acid. The protected cyanohydrin, which acts as an acyl carbanion equivalent in the cyclisation, fulfils an important role in this sequence because the stability of cyanohydrins to mild acid keeps the latent aldol systems (**76b**) protected until the final mild base step; also the stability of the cyanohydrin to oxidation is important during the olefin cleavage.

The second cyclisation method was by a group at the University of Rochester[59] who synthesised compounds of type **63** by constructing intermediate **79**, from the methyl thioether ketone **77** and the



75

R = CH(Me)OEt

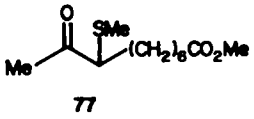


76

a: R_1 = C_8H_{17}, R_2 = CH(Me)OEt

b: $R_1 = CO_2Me$, $R_2 = H$.

ketene thioacetal monoxide **78**, which with 48% hydroborofluoric acid in acetonitrile afforded ketoaldehyde **80**. The latter then underwent cyclisation to the 4-hydroxycyclopentenone **63** (R = $(CH_2)_6CO_2Me$) at 40° in benzene with lithium hydroxide and a phase transfer catalyst (55% yield from **77**).



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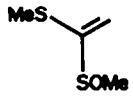

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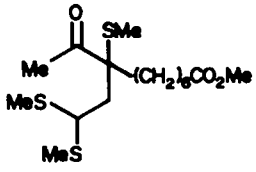

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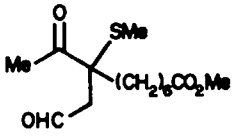
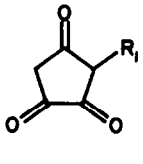


80

This method was also extended to the preparation of two other 4-hydroxycyclopentenones **63**, R=$(CH_2)_2Me$, $CH_2CH{=}CH_2$.

In two syntheses of hydroxyenones **67** (α-epimers) the 11-hydroxyl group was formed stereoselectively via a microbiological step. In the first of these methods by Sih *et al.*[60] the trione **81** was reduced stereospecifically with *Dipodascus uninucleatus* to the α-hydroxydiketone **82** which afforded enone **67** methyl ester (X = CH_2CH_2, α-epimer) via carbonyl reduction of the enolate **83** and an acid-catalysed allylic rearrangement.



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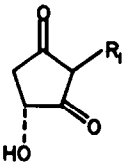

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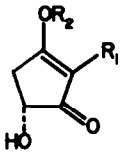


83

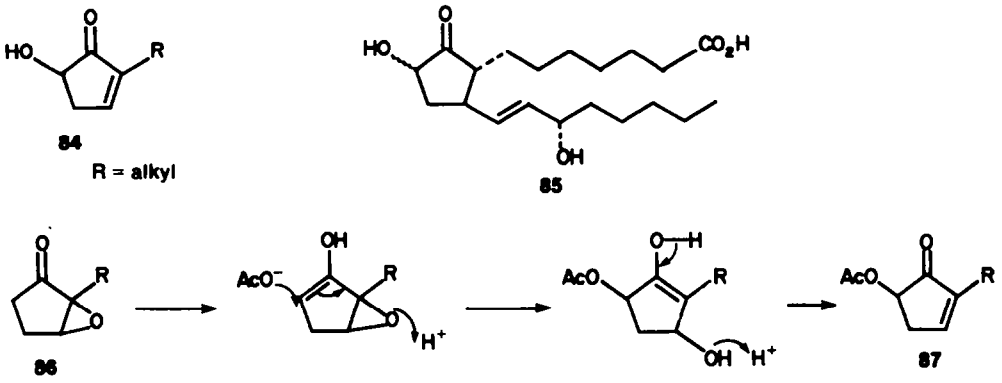
$R_1 = (CH_2)_6CO_2Me$

R_2 = IsOPr, PhCO

Interestingly, when the reduction of **81** was performed with *Mucor rammanianus*, the β-hydroxy epimer corresponding to **82** was obtained. In the second method, by a Japanese group,[61] the enone acid **37** (X = CH_2CH_2, R = CO_2H) was hydroxylated directly by *Aspergillus niger* (*Atce* 9142) to give **67** (X = CH_2CH_2, α-epimer) with partial asymmetric induction. The asymmetric reduction of compounds of type **81** to **82** has also been accomplished using lithium aluminium hydride partially decomposed by 3 equivalents of (−)-*N*-methylephedrine.[62,63]

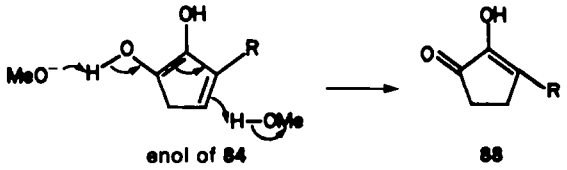
(d) *2-Alkyl-5-hydroxycyclopent-2-enones*

2-Alkyl-5-hydroxycyclopent-2-enones **84** were required for the application of the conjugate addition approach to the synthesis of 10-hydroxyprostaglandins **85**. May & Baker chemists[64,65] found that the acetyl derivative **87** of **84** could be prepared by heating the epoxides **86** of 2-alkylcyclopent-2-enones with acetic acid, a transformation which may be explained by the mechanism shown.

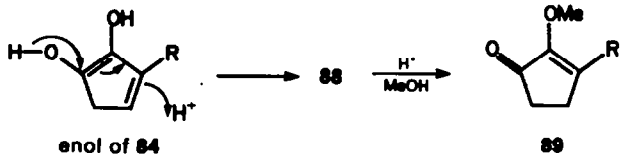


Hydrolysis to the free alcohol **84** was then achieved by careful treatment with sodium carbonate in aqueous methanol.

Interestingly, it was found that under strongly basic conditions—sodium methoxide in methanol—rearrangement to the 3-alkyl-2-hydroxycyclopent-2-enone **88** occurred, possibly by a mechanism such as:



A similar rearrangement took place when enone **84** was treated with methanolic hydrogen chloride, affording the methyl ether **89** of **88**, possibly as follows:



A similar type of epoxide cleavage was discovered by Vandewalle, Seghal and Sipido[66] with the epoxide of 2-methylcyclohexen-2-enone where treatment with 50% acetic acid afforded 6-hydroxyl-2-methylcyclohex-2-enone, and a transformation of this nature has also been noted in ring A of the steroids.[67] This reaction is clearly a potentially useful method for effecting what amounts to a nucleophilic attack at the α' site of an α,β-unsaturated ketone. However, more examples are required to establish whether the reaction is of broad generality.

STEREOSELECTIVE GENERATION OF CHIRAL CENTRES

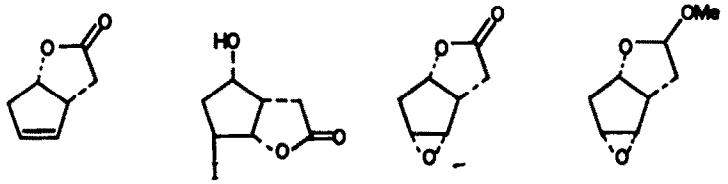
The existence of several chiral centres in the prostaglandin molecule presented a considerable synthetic challenge and a number of ingenious stereoselective methods have been devised. The discussion here is concentrated on some novel key reactions which have played an important part in this work, although in some cases reference is made to other stages in the syntheses where this is necessary to an understanding of the overall synthetic strategy.

(a) *Stereoselective generation and regioselective cleavage of cyclopentane epoxides*

A valuable approach arose from the finding that the C_{11} and C_{12} centres could be generated by a regioselective cleavage of cyclopentane epoxides which had been synthesised stereoselectively. In one of these syntheses, due to Corey *et al.*[20,68] the *cis–syn–cis* stereochemistry of the required epoxide **93** was achieved by epoxidation of the unsaturated lactone **90**, using 40% peracetic acid in acetic acid,† which gave a product containing 89% of the isomer **92** with the required configuration,

†This desired stereoselective epoxidation was only observed in an acetic acid medium.

and only 11% of the unwanted *cis–anti–cis* isomer. Alternatively, the lactone **90** was saponified and the product iodolactonised to iodolactone **91** which afforded **92** on lactone hydrolysis, cyclisation of the resulting iodohydrin and relactonisation.

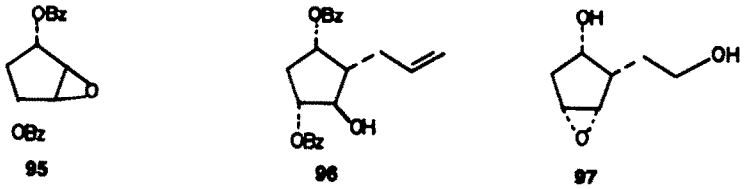


90 **91** **92** **93**

After conversion of epoxidolactone **90** to the cyclic acetal **93** (di-isobutylaluminium hydride treatment and methylation with boron trifluoride etherate in methanol), the desired regioselective cleavage of the epoxide was achieved by reaction with divinylcopperlithium (vinyl Gilman reagent) in ether at −20°, which gave the required intermediate **94a** as the major product, with only a minor amount of the alternative position isomer **94b** (**94a**:**94b** ratio 81:19).

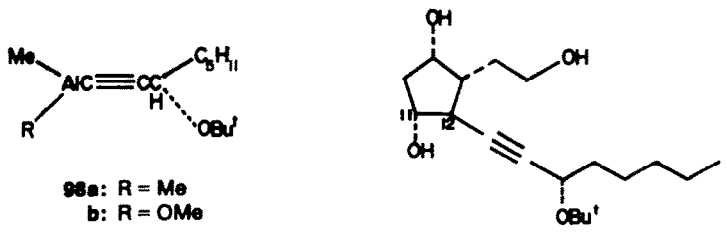
94a **94b**

In the second method by Fried *et al.*,[69–72] the diol epoxide **97** was synthesised stereoselectively by epoxidation of the dibenzyl ether of *cis*-cyclopentene-3,5-diol and thence reaction of the product **95** with lithium diallyl cuprate to give the *trans*-allyl alcohol **96**, tosylation, terminal hydroxylation of the olefin via the ozonide, debenzylation and epoxide closure with potassium hydroxide in methanol.



95 **96** **97**

Cleavage of **97** was achieved with the ethynylalane reagent **98** to give **99** as the exclusive product.



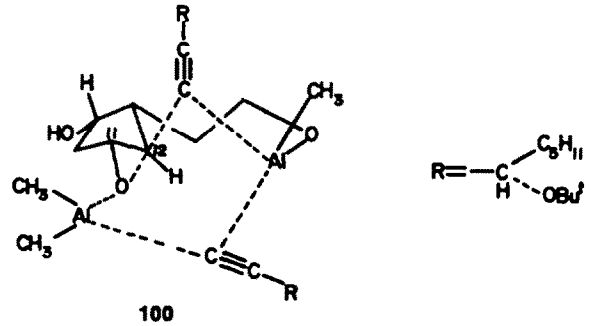
98a: R = Me
b: R = OMe

99

The high degree of regioselectivity in the formation of **99** was attributed to the directing influence of the primary alcohol function in **97** which can form a covalent bond with the aluminium in a cyclic transition state **100**, where the desired epoxide cleavage at C_{12} is preferred.

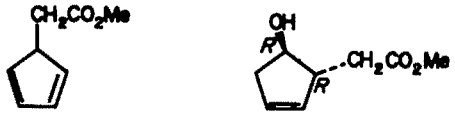
It was later shown[72] that this reaction depended upon the composition of the reagent and that the high degree of regioselectivity was obtained only when the dimethylchloroalane **98a** used contained methoxymethylchloroalane **98b** as a contaminant. Subsequent work was therefore carried out using the latter as the reagent.

Hoffmann–La-Roche chemists[73] have synthesised intermediate **90** in the required optically active



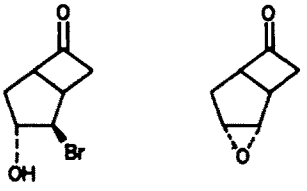
100

form, by treatment of the cyclopentadiene **101** with (+)-di-3-pinanylborane and then alkaline hydrogen peroxide to give the (−) hydroxyester **102**, which underwent cyclisation to optically pure **90** on base treatment of the mesylate. Intermediates **92** and **97** were then prepared from the resolved intermediate **90**, thus permitting a synthesis of prostaglandins in their optically active forms.



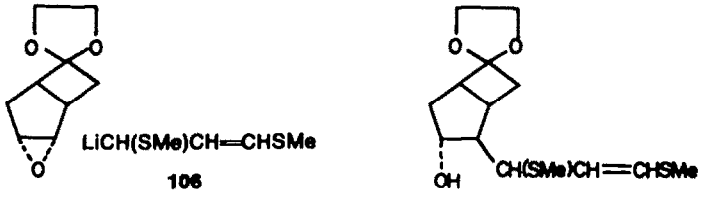
101 **102**

A synthesis of intermediate **93** has also been reported by chemists at Allen and Hanbury and Salford University[74] who treated the bromohydrin **103** with methoxide ion to give the epoxide **104**, which underwent photolysis in methanol, containing small amounts of sodium hydrogen carbonate and 2,5-dimethylhexa-2,4-diene, to give **93** (42%) and the corresponding endo isomer (11%).



103 **104**

Another interesting aspect of this epoxide cleavage reaction has been reported recently by the Allen and Hanbury and Salford University group[75] who found that their epoxide intermediate **105** was attacked with a high degree of regioselectivity by a wide variety of organometallic reagents, notably the methylthio lithium reagent **106**. Interestingly, the latter reagent showed a lack of selectivity when used to cleave epoxide **93**[68] but with **105** afforded a product containing 83% of the required isomer **107**.†

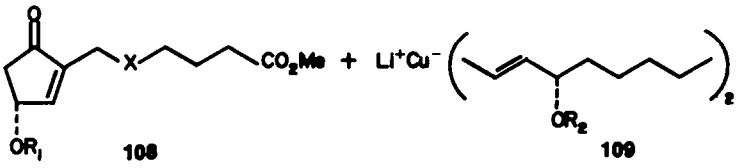


105 **106** **107**

(b) *Conjugate addition of organometallic complexes to cyclopentenones*

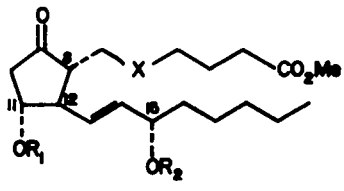
The formation of the prostanoic acid skeleton by conjugate addition to 2-alkylcyclopent-2-enones, e.g. **108**, referred to in Section 2 of this Report, has been achieved by several groups of workers using organometallic "ate" complexes, e.g. **109**,[56,60] **111**,[76] **112**.[77]

†This high regioselectivity is due to conformational control from the four-membered ring (S. M. Roberts personal communication).



108 109

R_1 = Thp, $OC(Me)_2OMe$ R_2 = $OCH(Me)OEt$, $Si(Me_2)^tBu$



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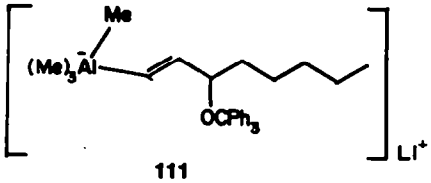
X = CH_2CH_2, CH=CH



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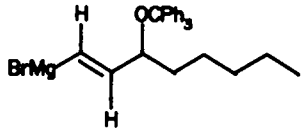
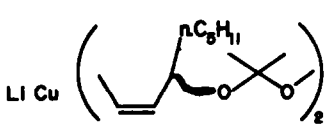


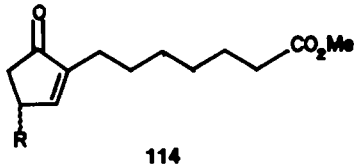
112

Sih *et al.*[56] showed that stereochemical control was attained in this reaction by virtue of the fact that the "ate" complexes, e.g. **109**, attack the enone **108** from the least hindered side of the cyclopentane ring, i.e. the side away from the grouping OR_1 with a high degree of stereoselectivity, and that the resulting enolate intermediate, on protonation, gives rise to the product **110** in which the two side chains are in the thermodynamically more stable *trans* relationship. Thus by starting off from the cyclopentenone **108** in which the group OR_1 has the required α-configuration, stereochemical control was achieved at all three centres C_8, C_{11} and C_{12}.

The correct stereochemistry at C_{15} could also be introduced here by starting off with the appropriate enantiomer of the "ate" complex **109**. However it has been shown, by Syntex workers,[78] that whereas racemic complexes of type **109** in which the double bond is *trans* afford, as would be expected, a mixture of both 15α and 15β isomers, the racemic reagent **113**, where the double bond is *cis*, yielded only the 15β product.[78,79] This was shown to be the case with the simple enone **114a** when reaction with intermediate **113** gave only one (**116a**) of the two theoretically possible products **115a** (15α) and **116a** (15β). Similarly with the enone **114b** where, because the group R is unresolved, a total of two racemic products might have been expected, only the (±) isomer (15β) **115b** was obtained.

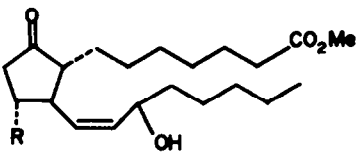


113



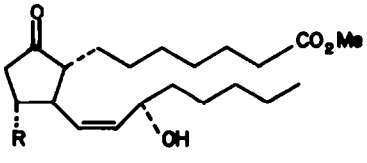
114

a: R = H
b: R = $OC(Me_2)OMe$



115

a: R = H
b: R = OH
c: R = OThp

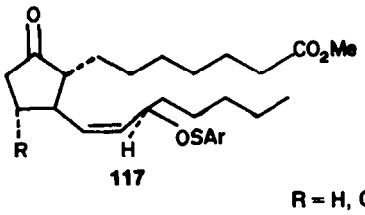


116

a: R = H
b: R = OH

This finding can only be the result of a stereoselective addition of the "*R*" enantiomer of **113** to C_3 of the β face of the enones **114** and of the "*S*" enantiomer of **113** to C_3 of the α face, the net effect being an asymmetric induction in which the newly created asymmetric centre (C_{15}) is 3 carbons removed from the locus of the original asymmetry. It is suggested that this stereoselectivity may be a consequence of co-ordination of the C-15 oxygen with copper producing a planar reagent with restricted rotation about the C_{14}–C_{15} bond, thereby favouring regiospecific attack on the enone through a co-ordinate intermediate.

This stereoselectivity, together with the fact that coupling of the *cis* intermediate **113** proceeded in a higher yield than the corresponding *trans* reagent, made this an attractive route to prostaglandins when it was found that the *cis* olefins **116** could be isomerised to the required *trans* compounds.[79] This was achieved via the sulphenate esters **117** which underwent a [2,3] sigmatropic rearrangement to give the sulphoxides **119**, the latter giving prostaglandin derivatives of natural configuration **120** on treatment with trimethylphosphite in methanol. This rearrangement was stereospecific, this being anticipated from the fact that it would be expected to proceed through the thermodynamically more stable transition state which resembles conformer **118** more than **117** and thus provides the desired geometric and chiral inversions. In practice sulphoxides **119** were formed directly when the intermediate **115** was treated with three equivalents of triethylamine and *p*-toluenesulphonyl chloride.



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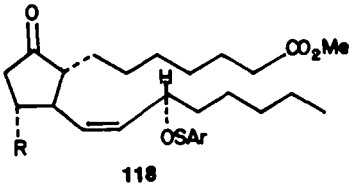
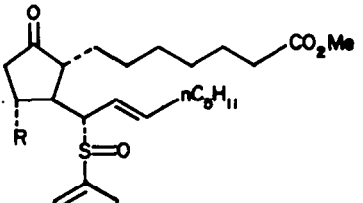
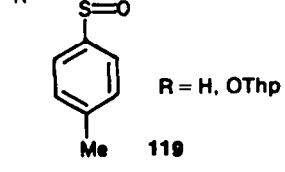


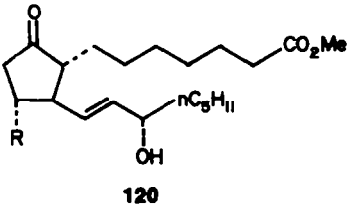
118

R = H, OThp



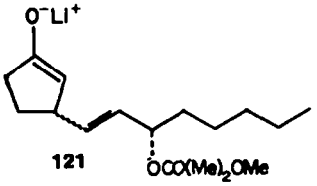


119



120

Organometallic conjugate addition reactions have also been employed in conjunction with alkylation of a trapped cyclopentane enolate.[80-82] Thus in a synthesis of 11-deoxyprostaglandins, Patterson and Fried[80] first constructed the prostaglandin ω-chain by reaction of cyclopent-2-enone with the organocopper reagent **122** and then trapped the enolate anion **121** of the product with trimethylsilyl chloride, to give silyl enol ether **123**, which underwent alkylation with *cis*-7-bromo-5-heptenoate to yield a mixture of 11-deoxy-PGE_2 **124** and 11-deoxy-8,12-*epi*-PGE_2 **125** methyl esters.



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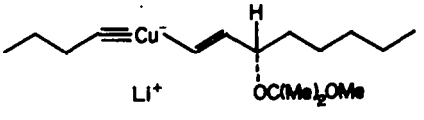

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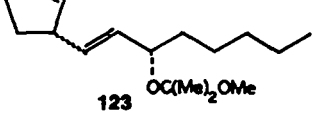

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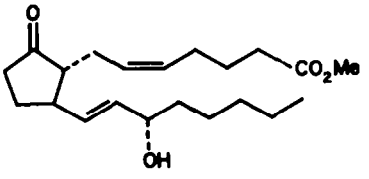
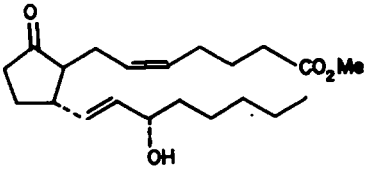
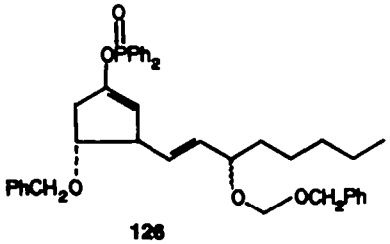


124



125

Stork and Isobe[81,82] used an organometallic complex to insert carbons 1–6 of the α-chain by a conjugate addition to the α-methylene cyclopentanone **128**. The latter, which was synthesised by forming the enolate **126**, trapping with formaldehyde to give the hydroxymethylene compound **127** and then elimination of water, underwent addition to the divinyl cuprate from the vinyl iodide **130** to give the prostaglandin precursor **129** with the required stereochemistry at C_8, C_{11} and C_{12}.



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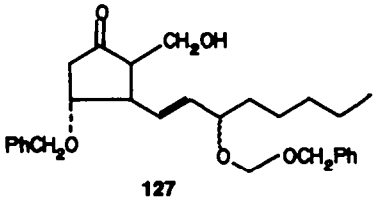

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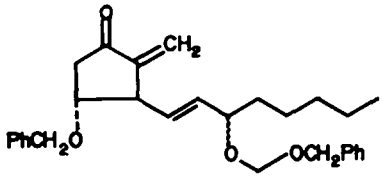

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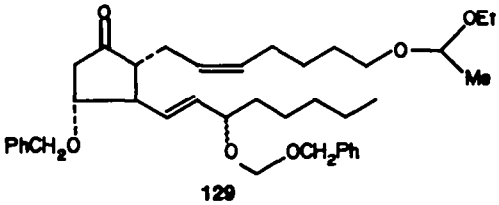
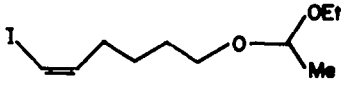


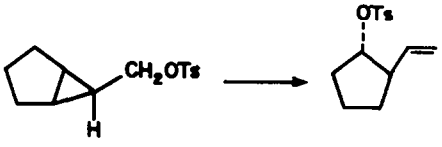
129



130

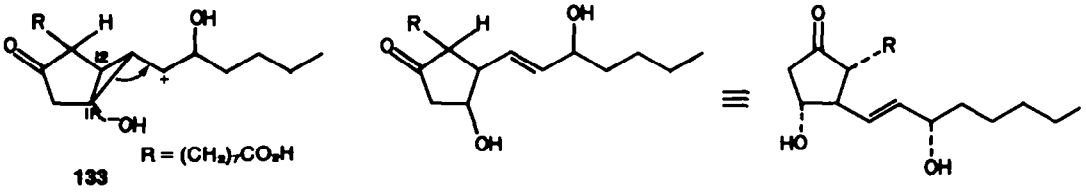
(c) *Solvolysis of cyclopropyl cations*

In an approach to prostaglandins originated by Just and Simonovitch of McGill University and much developed by Upjohn chemists, the chiral centres at C_{11}, C_{12}, C_{15} together with the C_{13}, C_{14} *trans* double bond were generated by a method based upon the cleavage of an appropriate bicyclo[3.1.0]hexane.[83–90,92] It had been known from the earlier work of Wiberg and Ashe[91] that a simple bicyclo[3.1.0]hexane tosylate **131** will undergo solvolysis with potassium acetate and acetic acid to give a ring-opened compound **132**.



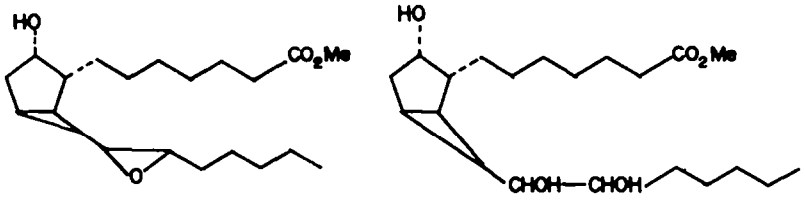
131 **132**

The extension of this to the prostaglandin situation was based upon the principle that, in the solvolysis of the appropriate cyclopropylcarbinyl cation **133**, the hydroxyl ion attack might be expected to occur at C_{11} because steric interaction would hinder approach to the alternative position C_{12}. Also, formation of the *trans* double bond might be expected as a consequence of the spatial disposition of substituents during the ring-opening sequence.



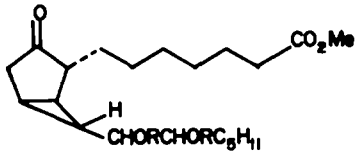
133

The cyclopropinyl cation was originally generated[83,84] from an epoxide, e.g. **134** which underwent acid-catalysed opening with formic acid or trifluoroacetic acid to give, on hydrolysis of the formate esters with sodium carbonate, the desired prostaglandin ($PGF_{1\alpha}$ methyl ester) and its C_{15} epimer.



134 135

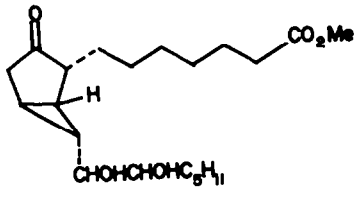
However, the yields of $PGF_{1\alpha}$ methyl ester here was very low (2–3%), the major products being the *vic*-glycols **135**. This was possibly because the presence of an oxygen function adjacent to the developing cyclopropylcarbinyl cation acts to stabilise the charge on that carbon, reducing the degree of delocalisation into the cyclopropane ring, and so decreasing the extent of nucleophilic attack on the ring, thus promoting glycol formation. In subsequent work the glycols, e.g. **136a**, prepared by dihydroxylation of the olefin, were converted to the bismethanesulphonates **136b** and the latter solvolysed in acetone-water to give the (±)prostaglandin methyl ester (yields 4–8%) together with the C_{15} isomer.[85] However the major products were the unrearranged glycol 15-monomesylates resulting from the hydrolysis of only the cyclopropylcarbinyl mesylate.



136

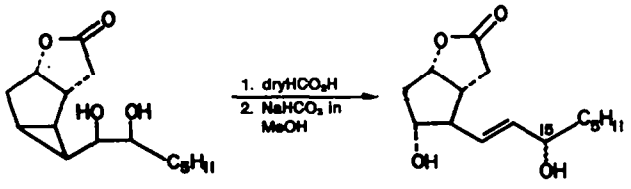
a: R = H
b: R = SO_2Me

Interestingly, however, the glycol intermediates e.g. **137** having the *endo*-configuration at C_{13} gave higher yields of the prostaglandin (17–19%) by this method.[86,87]



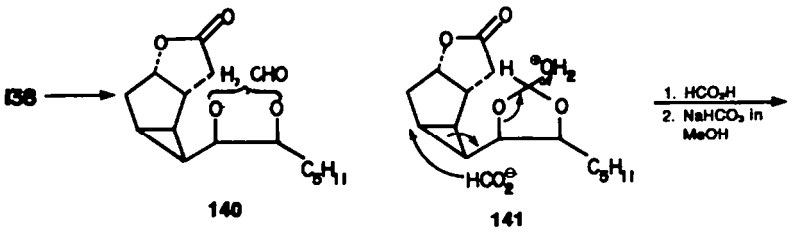
137

In later work[89,90] it was found that improved results could be obtained by proceeding through orthoester intermediates and this also led to a method for effecting stereocontrol at C_{15}. This development arose from the observation that opening of the cyclopropyl carbinyl system in intermediate **138** with formic acid followed by methanolysis gave the best results only when anhydrous formic acid was used, and that the yield of the ring-opened product **139** was substantially reduced by the presence of small concentrations of water.[90]



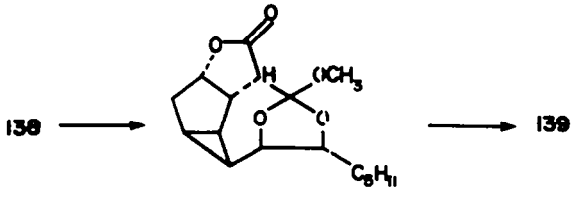
138 139

It was suggested that this observation was consistent with the formation of a monoformate **140** which cyclised to an orthoester intermediate **141**.



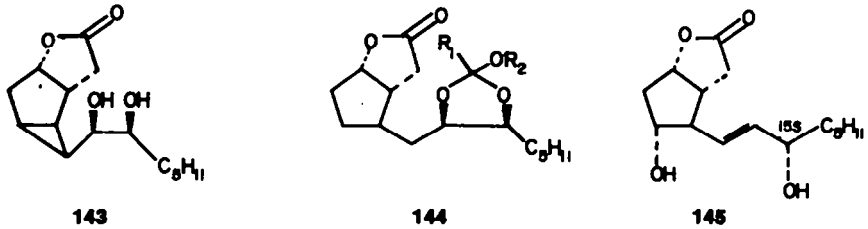
140 141

This hypothesis was tested by synthesising orthoester **142** and treating it with dry formic acid followed by methanolysis with methanol and sodium carbonate when the ring opening was found to be complete in less than 5 min, whereas openings of the glycol **138** in formic acid required about 3 hr. This method was also much cleaner, giving fewer side products and a higher overall yield of the desired product **139** (~70% compared to ~60%).



142

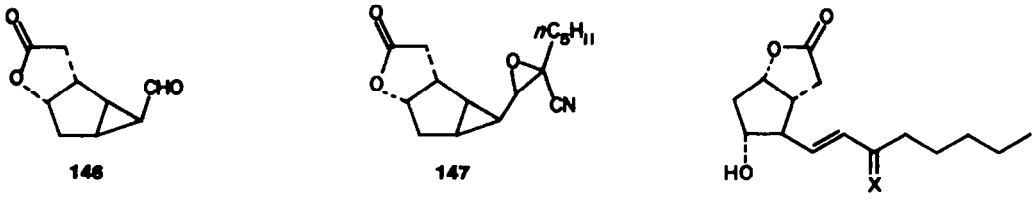
The possibility of effecting stereocontrol at C_{15} followed from the conclusion that since the carbon–oxygen bond at C_{15} is not cleaved in this reaction, the C_{15} stereochemistry of the precursor should be retained in the opened product. The 15S orthoformate **144a** was therefore prepared, from the resolved diol **143**, and subjected to the formic acid and methanolysis treatment, when it was found that the C_{15} stereochemistry had in fact been retained to a large extent, the major product being the 15S compound **145**. However some of the 15R stereoisomer was also found to be present in the product as a result of epimerisation, this being ascribed to the solvolysis of the allylic formate, since re-introduction of **145** to formic acid resulted in increasing loss of stereochemical integrity with time. However, using the orthopropionate **144b**, which would be expected to generate allylic esters less labile than formates to solvolysis, the desired complete retention of the 15S stereochemistry was achieved.



143 144 145

a: R_1 = H, R_2 = Me
b: R_1 = R_2 = Et

A cyclopropane cleavage, in the epoxido nitrile intermediate **147** has been employed in a synthesis of the 15-ketone **148b** corresponding to alcohol **145**.[92] The epoxido nitrile **147**, which had been prepared from the aldehyde **146** by reaction with α,α-dibromoheptane nitrile and hexamethylphosphorous triamide, underwent solvolysis in formic acid and then formate hydrolysis in dilute sulphuric acid to the

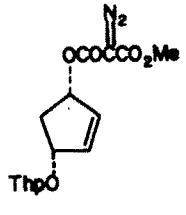


146 147

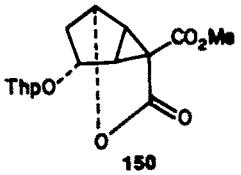
148 a: X = OH, CN
b: X = O

cyanohydrin **148a**. The yield here was high, (73.8% overall)† from aldehyde **146** to the free ketone **148b** obtained by hydrolysis (1N sodium bicarbonate in ethyl acetate) of cyanohydrin **148a**.

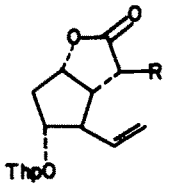
Cleavage of a cyclopropane ring fused to a cyclopentane has also featured in prostaglandin syntheses by other groups.[93-97] Corey and Fuchs[93] showed that the cyclopropane ring in bicyclohexane intermediates can be opened in satisfactory yields by homoconjugate addition of divinylcopperlithium. Thus the bicyclohexane **150**, which was prepared by thermolysis with copper powder of the diazoester **149**, underwent cleavage with divinylcopperlithium to give the lactone **151a** which on decarboxylation with lithium iodide in pyridine gave the lactone **151b** in 37% yield (not optimised), having the correct stereochemistry at C-8, C-9, C-11 and C-12.



149

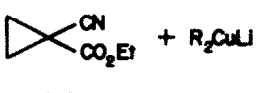


150

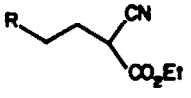


151 a: R = CO_2Me
b: R = H

Some idea of the generality of this addition process with organocopperlithium reagents was obtained by showing that ethyl α-cyanocyclopropanecarboxylate **152** with dimethyl or divinylcopperlithium afforded the α-cyanoesters **153a** and **153b** in 75 and 70% yields respectively, and that these reagents effected opening of the cyclohexyl analogue **154** of **150** to give **155a** and **155b** each in 60% yield.

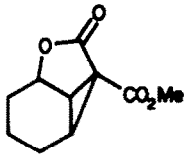


152

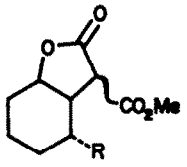


153

a: R = Me
b: R = CH=CH_2



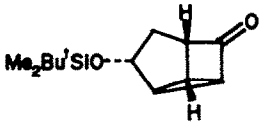
154



155

a: R = Me
b: R = CH=CH_2

Chemists at Allen & Hanbury and the University of Salford[94] effected a cleavage of the tricycloheptanone system **156**, which had been prepared by base-induced cyclisation of the bromohydrin **103**, with the mixed organocuprate reagent **157** to give the norbornanone **158** (88% yield) in which the stereochemistry at the centres C-8, C-9, C-11 and C-12 had been established.



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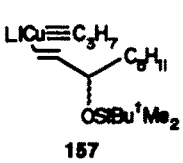
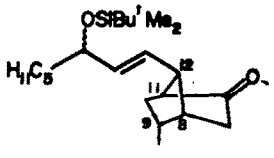


157

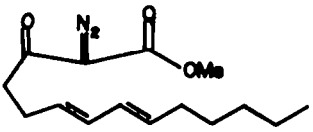


158

OSiBu'Me_2

Sagami chemists generated the chiral centre at C_{15} stereoselectively in the 11-deoxyprostaglandin series by an interesting cleavage of the bicyclo[3.1.0]hexane **160**.[95-97] This intermediate, which was prepared stereoselectively by thermolysis of the diazo-compound **159**, underwent stereospecific ring opening with potassium thiophenoxide in t-butanol to give the 2,3-disubstituted cyclopentanone **161** in

†GLC assay.



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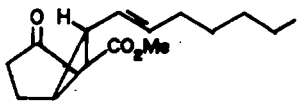

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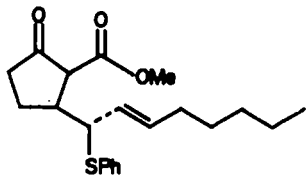
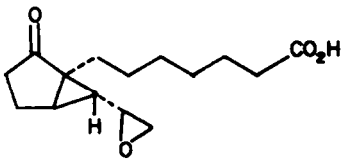


161

89% yield, the latter then affording 11-deoxy-PGE_1 via a sulphoxide rearrangement similar to that described for intermediate **119**. A similar type of cleavage has been reported by Taber.[98]

In a synthesis of 11-deoxyprostaglandins, Melnikova, Grigorev and Pivnitsky[99] effected ring opening of the cyclopropane ring in the epoxide intermediate **162** with lithium in liquid ammonia to give, after esterification, a stereoisomeric mixture of ketones **164** which afforded the ketoaldehyde **163** on oxidation with chromium trioxide in pyridine–methylene chloride.



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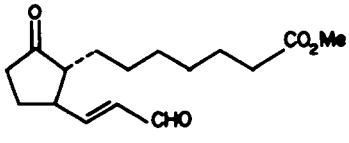
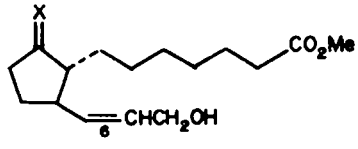


163

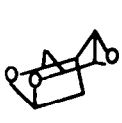


X = O, H, OH

164

(d) *Construction and cleavage of internally protected cyclohexanes*

A synthesis developed at the Woodward Research Institute at Basel,[100,101] based on the construction and cleavage of internally protected cyclohexanes, incorporates a number of interesting reactions. The epoxide **165** was prepared, as the major product from the corresponding olefin, by the action of a reagent prepared from hydrogen peroxide, benzonitrile and potassium bicarbonate in methanol, preferential attack occurring at the concave side of the molecule. Because of the rigid conformation of the molecule, the epoxide ring of **165** underwent regiospecific cleavage on ammonolysis with aqueous ammonia to give the diaxial alcohol **166** in a yield of more than 90%. The latter was converted with methanolic hydrogen chloride to the dihydroxy-amino alcohol hydrochloride **167** which has a flexible skeleton and thus allows a conformational change to take place leading to a situation in which the amino group is equatorially positioned and appropriately set up as a leaving group. This allowed a ring contraction step to take place, accomplished by diazotisation with sodium nitrite in sodium acetate-acetic acid, followed by neutralization with mild base, to give the cyclopentane aldehyde **168**. The latter intermediate, well known from the work of Corey, contains the correct stereochemical features of the prostaglandin at C-8, C-9, C-11 and C-12.



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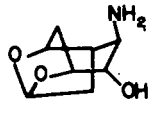

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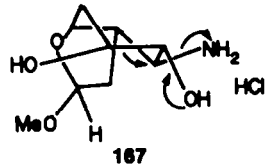

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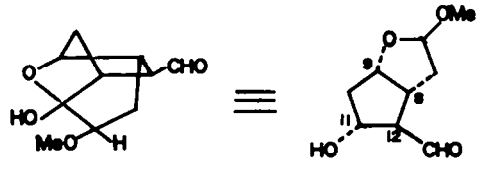
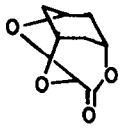


168

The olefin precursor of the epoxide **165** was synthesised from the tricyclic lactone **169**, prepared from *cis*-cyclohexane-1,3,5-triol, which was converted in three steps—borohydride reduction, mesylation and base treatment—to give the olefin mesylate **170a**, the latter undergoing sololysis to give the tricyclic carb-

inol **171a**, and thence mesylation and elimination. Interestingly the cyclisation **170a** → **171a** gave only 5–8% of the alternative product **172a**, whereas it had been known previously that the corresponding carbocyclic compound **170b** when hydrolysed in 80% aqueous acetone gave **172b** as the major product (95% yield). This difference in mode of action may be attributed to the inductive effect of the oxygen in the allylic position to the double bond in **170a** by concentrating π electrons at the closer carbon of the double bond, thus increasing its nucleophilicity. The same effect would also be expected to destabilise the otherwise stereochemically preferred 2-adamantyl carbonium ion and lead to the same result.



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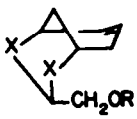
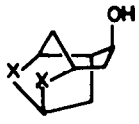


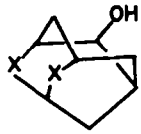
170

a: X = O, R = Ms
b: X = CH_2, R = Ts



171

a: X = O
b: X = CH_2



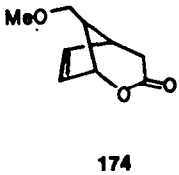
172

a: X = O
b: X = CH_2

(e) *Cleavage of Diels–Alder adducts*

Many prostaglandin syntheses have converged on lactols of type **168**, or their derivatives. In the original approach to these intermediates, by Corey *et al.*[22,102] they were constructed from the lactone **174** which had been obtained via Baeyer–Villiger oxidation of the Diels–Alder adduct **173** by reaction with potassium tri-iodide to give the iodolactone **176** and then deiodination with tri-*n*-butyltin hydride. They have been prepared in the required optically active forms by resolution of the acid **175** corresponding to lactone **174** or by synthesising a bicyclic intermediate of type **173** via asymmetric induction.[103]

173



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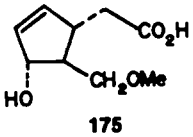

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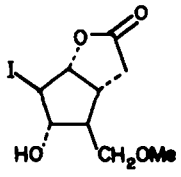

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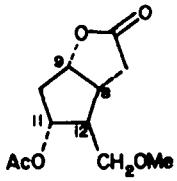
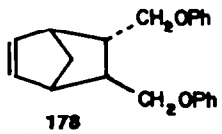


177

Several groups[104–107] have constructed appropriately substituted bicycloalkenes, e.g. **178** (ICI) by Diels–Alder addition reactions and then taken these forward to intermediates of type **179** via cleavage of the double bond. These generally employed standard reactions but an important feature of this work was the finding that the *cis*-1,3-cyclopentandialdehydes **179a** formed from the cleavage can be transformed, with complete retention of stereochemistry, by means of a Baeyer–Villiger reaction on the corresponding diacetyl compounds **179b**, to form the C-9 and C-11 oxygen functions of the prostaglandin in **179c**.



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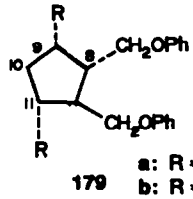
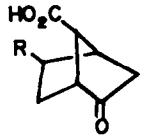


179

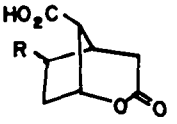
a: R = CHO
b: R = Ac
c: R = OAc

Workers at Pfizer[108] and the University of Manchester[109] prepared intermediates of type **168** by an interesting stereo- and regioselective ring opening of the nortricyclane **180** which had been prepared via a Prins reaction of norbornadiene and paraformaldehyde in formic acid.

180

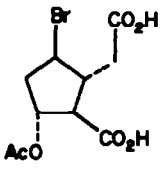


181 a: R = Cl
b: R = Br

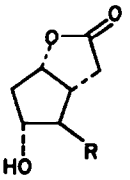


182 a: R = Cl
b: R = Br

The ring opening was accomplished with aqueous hydrochloric acid[108] or with hydrogen bromide in acetic acid[109] to give intermediates **181a** and **181b** respectively. After Baeyer–Villiger oxidation to **182b** the γ-lactone **184** was established via the bromo-dicarboxylic acid **183** (hydrogen bromide in acetic acid) which yielded **184b** with aqueous sodium hydroxide. An interesting feature of this work was that the overall conversion **181b** → **184b** could be carried out as a one-pot process by adding sulphuric acid to the Baeyer–Villiger reaction mixture and working up the product with alkali.[109]



183

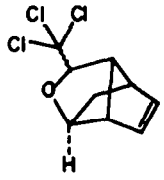


184

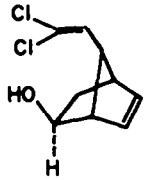
a: R = CH_2OThp
b: R = CO_2H

A similar conversion of **181a**, after replacement of the carboxylic acid and a tetrahydropyranloxy group, was accomplished using aqueous base with hydrogen peroxide buffer to give **184a**.

A bicyclic intermediate **187** of type **180** has been prepared by a group at Tohoku University[110] from the tricyclic compound **185**, which is available from reaction of norbornadiene and chloral in the presence of aluminium chloride. Zinc and acetic acid treatment of **185** afforded the bicyclic ketene dihydrochloride **186** of which the tosylate with potassium acetate in acetic acid afforded the tricyclic acetate **187** as an epimeric mixture.



185



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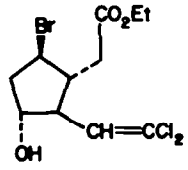
187



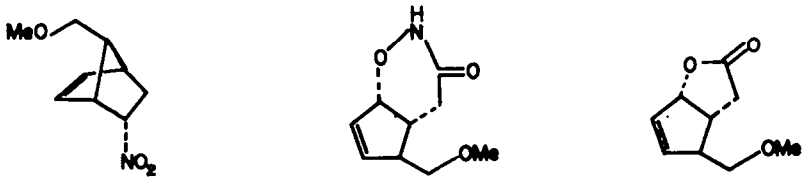
188

Interestingly these workers found that the intermediate **188**, prepared from **187** via methods similar to those used in the preparation of **183** from **180**, could not be converted to the lactone of type **184** by hydroxide ion, but they managed to achieve this transformation under solvolytic conditions using mercuric acetate or silver perchlorate as a catalyst.

Chemists at the Indian Institute of Technology, Kanpur, prepared lactone intermediates via a nitrous oxide extrusion from nitrobicycloheptenes.[111,112] This reaction took place on treatment of the sodium salt of nitro compound **189** with hydrochloric acid giving a mixture of the lactone **191** and the cyclic hydroxamic acid **190** which could be transformed to **191** with nitrous acid. The intermediate **191** is a precursor of the A prostaglandins.

(f) *Regiospecific addition of formaldehyde to a cyclopentenone by a prins reaction*

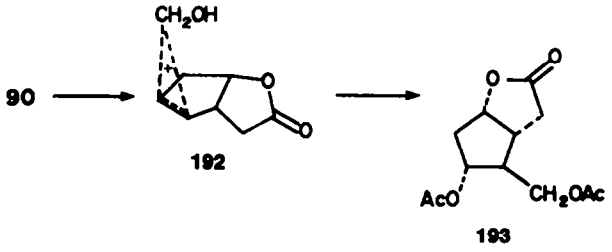
Another way of introducing the C-11 and C-12 functionalities was devised by a Hungarian team[113] who found that a Prins reaction on lactone **90**, using excess paraformaldehyde monomerised *in situ.* with



189 190 191

sulphuric acid in glacial acetic acid, took place at 60–80° affording the intermediate **193** regio- and stereospecifically, in 75–85% yield.

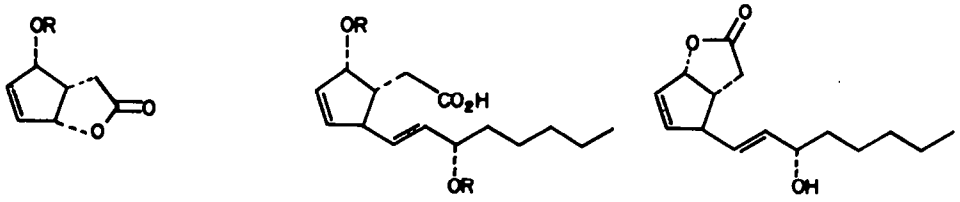
The formation of **193** may be accounted for by preferential opening of the putative intermediate three-centre carbonium ion **192** at the sterically less hindered position.



192 193

(g) *Stereocontrolled cross coupling of a vinylic copper reagent with an allylic electrophile*

Corey and Mann[114] prepared the lactone **196**, an intermediate in a PGA_2 synthesis, via a cross coupling of the vinylic copper reagent **109** ($R_2 = SiMe_2{}^tBu$) to the unsaturated lactone **194**, affording hydroxy acid **195**. This reaction was noteworthy for the high degree of stereochemical control enforced by the dimethyl-*t*-butylsilyl screening group in **194** and for the fact that the stereochemical outcome is determined by the presence of an anionic leaving group, introduced with rigid stereochemical control which is prone to attack by an organometallic nucleophile at carbon (inversion), rather than at the group itself. The product **195** then gave lactone **196** on heating in acetone-hydrochloric acid.



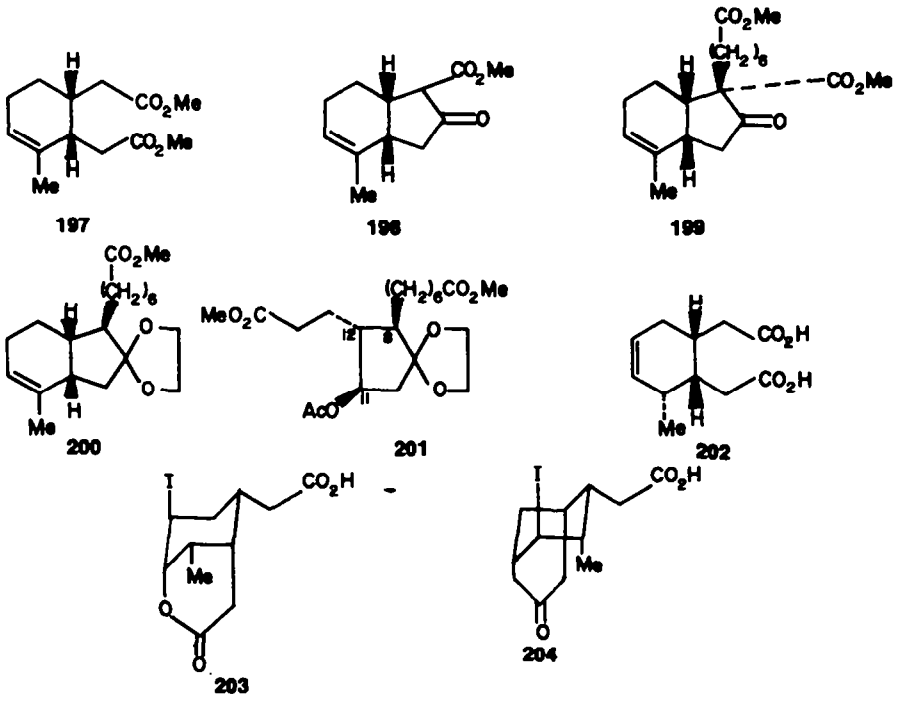
194 195 196

R = Si(Me₂)ᵗBu

(h) *Cleavage of hydrindenes*

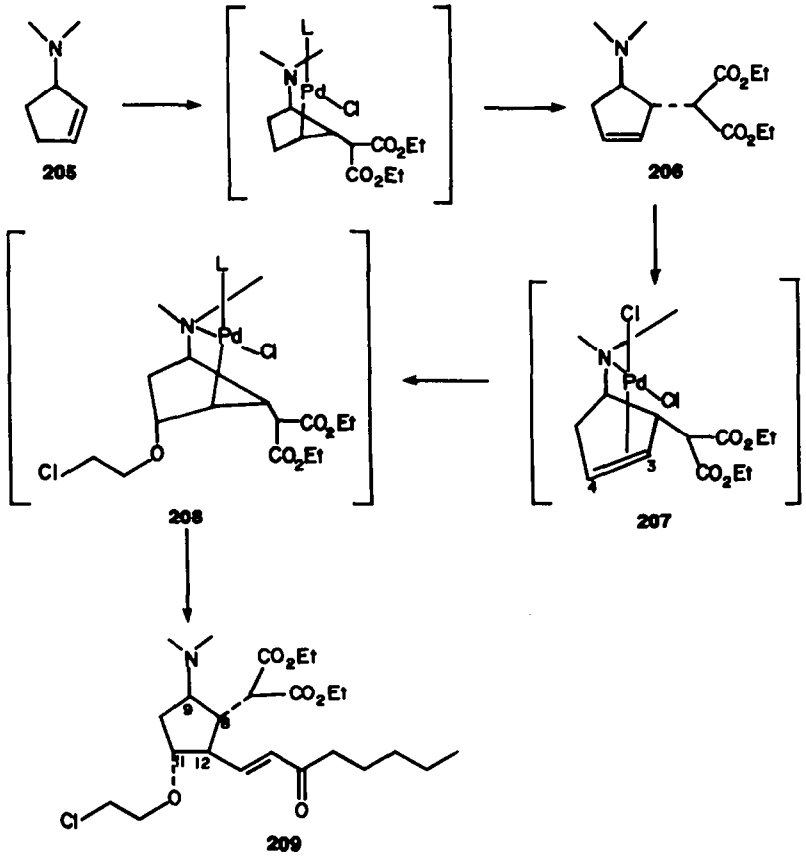
In a synthesis by Merck chemists,[115,116] the required stereochemistry at C-8, C-11 and C-12 in intermediate **201** was arrived at by construction and olefinic cleavage of a hydrindene system **200** and then isomerisation of the generated acetyl group, esterification and Baeyer–Villiger oxidation. Some interesting selective reactions arose in the synthesis of **200** from the cyclohexane **202**. When the latter was subjected to an iodolactonisation reaction in sodium carbonate solution with iodine–potassium iodide, only one (**203**) of the two theoretically possible products **203** and **204** was formed. This singularity in directional course of lactone formation is attributed to the optimisation of conformational effects. The same specificity in the direction of cyclisation was also observed on treatment of intermediate **202** with N-bromosuccinimide in *t*-butyl alcohol which afforded exclusively the bromolactonic acid corresponding to **203**.

These stereoselective reactions paved the way to the synthesis of the cyclohexene **197** via dehalogenation, lactone cleavage and dehydration. Intermediate **197** then underwent, for steric reasons, a undirectional Dieckmann closure to the hydrindone **198**. Alkylation of **198** to the β-keto diester **199** also proceeded stereoselectively affording, via decarbomethoxylation (lithium iodide in collidine), the ketone corresponding to **200** in an exo/endo ratio of 6:1.

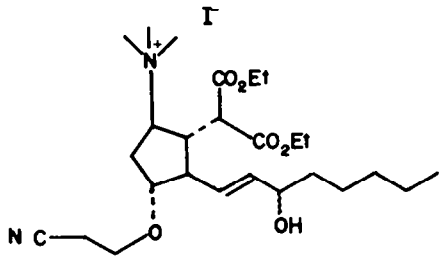


(i) *Synthesis via carbopalladation*

Holton[117] developed an efficient and short prostaglandin synthesis in which the chiral centres at C-8, C-9, C-11 and C-12 were constructed via carbopalladation of a cyclopentene. It was found that treatment of cyclopentenylamine **205** with lithium tetrachloropalladate (LTP) and sodium diethyl malonate in THF and then with di-isopropylethylamine afforded the isomerically pure malonate **206** in 92% yield.



Treatment of **206** with LTP in a mixture of 4:1 β-chloroethanol-dimethylsulphoxide containing di-isopropylethylamine gave rise to a palladium complex, presumably **208**, which was treated with *n*-pentyl vinyl ketone in DMF–benzene to give the enone **209** as the predominant product (50% yield).



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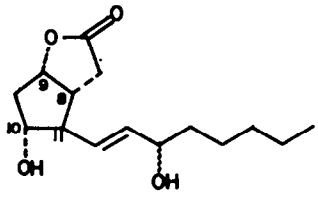


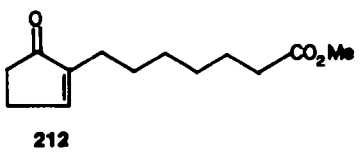
211

The selection of β-chloroethanol in this reaction was determined in part by the need to have an alcohol with sufficient bulk so that interference with the adjacent malonyl moiety would direct addition to the intermediate complex **207** exclusively at position 4.

Intermediate **209**, which has the required stereochemistry at C_8, C_{11} and C_{12}, was taken forward to the lactone intermediate **211** via the quaternary iodide **210** and treatment with potassium hydroxide.

(j) *Cleavage of a bicyclo*[3.2.0]*heptane prepared by a mixed photoaddition of two unsaturated ketones*

Ayerst chemists[118] described an interesting synthesis of 13,14-dihydro-11-deoxyprostaglandins based upon the formation of a bicyclo[3.2.0]heptane **214a** by a mixed photoaddition of two unsaturated ketones **212**, **213**.



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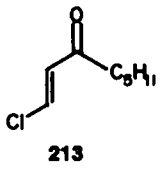

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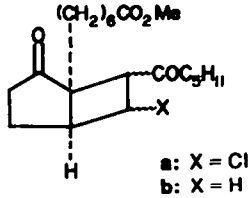
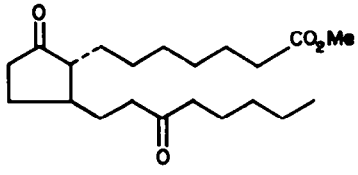


214

a: X = Cl
b: X = H

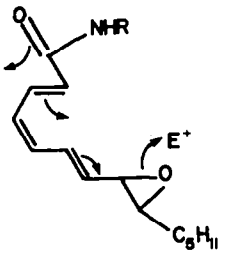
The photo adduct **214a** underwent fragmentation with zinc–acetic acid to give a mixture of the desired prostaglandin intermediate **215**, together with some of the dehalogenated cyclobutanone **214b** which could be transformed to **215** on further zinc-acetic acid treatment. As in a number of other syntheses, the *trans* geometry of the side chains in **215** arose for steric reasons



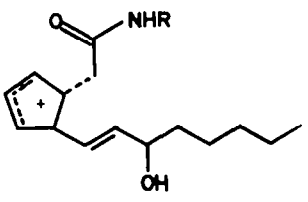
215

(k) *Cyclopentane formation by novel intramolecular cyclisations*

Some prostaglandin syntheses have been based upon a step in which an appropriately substituted cyclopentane intermediate is formed directly by cyclisation of an aliphatic intermediate. A noteworthy example of this approach was described by Corey, Fleet and Kato [119] in which the intermediate **218** was formed from the epoxytrienamide **216** by a cyclisation of the pentadienyl cation ⟶cyclopentyl cation type. This reaction was carried out in a 2-nitropropane, 1-nitropropane mixture by treatment with potassium biphthalate to afford the lactone **217** as a mixture of C-15 OH epimers. Although the yield of **217** was low (15%) this reaction is of particular interest for the manner in which the acetyl amide side chain in the intermediate allylic cation **217a** acts as a potential neighbouring group which can deliver an oxygen substituent to C-9 and simultaneously control the *cis* arrangement of the substituents at C-8 and C-9.

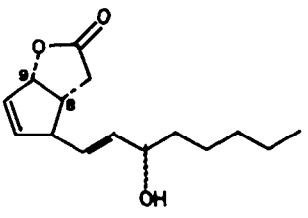


216



217a

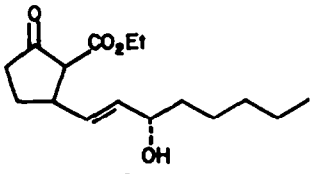
R = *p* – $C_6H_5C_6H_4$



217

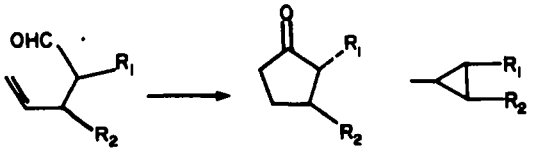
A related cyclisation was described by Roussel–Uclaf chemists in which the pyrrolidine enamine of the β-epoxy olefin **218** afforded the cyclopentanone **219** by the action of sodamide.[120]

218



219

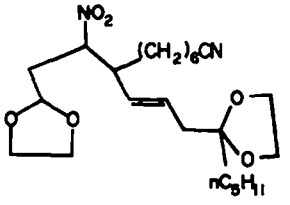
Sankyo chemists[121] achieved a cyclisation of the unsaturated aldehyde **220** to prostanoic acid methyl esters **221A** with stannic chloride in nitromethane at room temperature (42% yield). This reaction, which was also carried out on aldehydes **220** with several different substituents R_1 and R_2, is understood to be the first example of direct cyclisation of an alkan-1-al-4-ene system to a five membered ring ketone. Interestingly, these workers also showed that tris(triphenylphosphine)chlororhodium converts intermediates **220** to a mixture of **221A** and the cyclopropane derivative **221B** formed by decarbonylation. Several examples of these reactions are quoted with various values for R_1 and R_2.



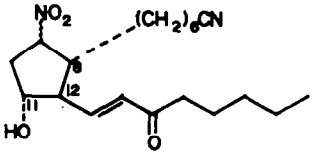
220 221A 221B

$R_1 = (CH_2)_6CO_2Me$,
$R_2 = (CH_2)_7Me$

In earlier work Corey *et al.*[122] reported that the nitro ketal **222** underwent cyclisation with stannic chloride in acetone to give the prostanoic acid derivative **223** essentially free of the 11β-hydroxy epimer.



222

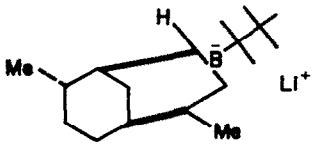


223

(l) *Stereoselective reduction of α,β-unsaturated ketones*

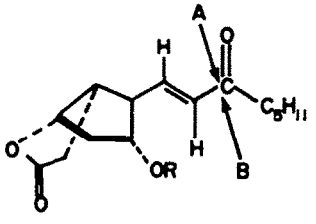
The generation of the ω-chain allylic alcohol system in prostaglandins by reduction of an α,β-unsaturated ketone (**34**; Section 1i) not unexpectedly affords a mixture of both 15α and 15β epimers, since the hydride type reagents normally used can approach the point of attack from any direction. However, Corey *et al.*[123] devised an ingenious procedure for achieving stereochemical control in which a linear directing group, e.g. *p*-phenylbenzoyl, was attached to the adjacent cyclopentane ring oxygen in **34**,

the reduction being carried out with a bulky borohydride reagent e.g. thexyl borane (±)-limonene **224** [prepared from thexyl borane, (±)-limonene and *t*-butyl lithium] at $-ca.$ 120°.

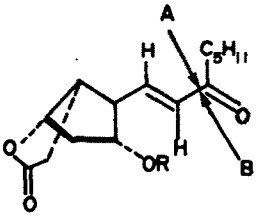


224

At the low reaction temperature employed, the molecule is frozen in a conformation in which the *p*-phenylbenzoyl group is lined up alongside the enone side chain with which it is able to assume Van der Waals contact; thus blocking the approach of the reagent from one side of the molecule. Attack of the reagent therefore occurs from the opposite side and would be expected to give the desired 15S alcohol, provided the enone is in the s-*cis* configuration **225**. The latter conformation, in which four adjacent atoms of the C_6H_4 unit of the *p*-phenylbenzoyl group can be placed directly in contact with the enone unit, is in fact favoured over the alternative s-*trans* form **226** and the reaction is therefore set up for the desired stereocontrol. Using this procedure the ratio of 15S to 15R alcohols obtained from the reduction was 82:18.



s-*cis* enone configuration
225



s-*trans* enone configuration
226

R = CO·C_6H_4·C_6H_5·*p*
NH·C_6H_4·C_6H_5·*p*

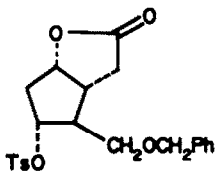
attack from
A gives 15S
B gives 15R

A gives 15R
B gives 15S

In a further development of the method the *p*-phenylbenzoyl group R was replaced by the *p*-phenylphenylcarbamoyl grouping which gave better contact with the s-*cis* enone side chain. This is because the urethane unit of this grouping can adopt a conformation which avoids an undesirable steric interference which occurs between the benzylic CH_2 group of the ester and the hydrogen attached to C-11 of the cyclopentane ring. Application of this refinement raised the ratio 15S:15R to 92:8.

(m) *Nucleophilic inversion of hydroxyl groups at asymmetric centres*

Methods for effecting the inversion of stereochemistry at hydroxylic centres are of obvious importance in prostaglandin chemistry as a means of preparing various stereoisomers from more readily available intermediates of the opposite configuration. Corey and Terashima[124] found that inversion at C-11 could be effected by treatment of the tosylate **227** with tetra-*n*-butylammonium formate in acetone giving mainly the formate **228**, together with a minor amount of the elimination product **229** (ratio 75:25, 97% total yield). Interestingly when tetra-*n*-butylammonium oxalate was used in place of the formate, the unsaturated compound **229** was the sole product (82% yield) and in fact this reagent proved to be an excellent nucleophile for effecting elimination with substrates, such as **227** under very mild conditions. With tetra-*n*-butyl ammonium acetate the ratio of **228b** to **229b** was 1.2:1. It is suggested that the preference for the elimination over substitution in the oxalate may be a result of a possible "bidentate" attack on hydrogen which should be especially favourable, since it leads to the oxalate mono acid ion **230** which is stabilised by hydrogen bonding. The stability of **230**, which can be reflected in the transition state for elimination, provides no driving force for nucleophilic substitution at carbon. The greater tendency for substitution at carbon by formate ion relative to acetate ion, may be a result of the smaller size of the former or its smaller basicity (at hydrogen) or to both. Use of this method of inversion has been further developed by Floyd, Crosby and Weinshenker.[125,126].



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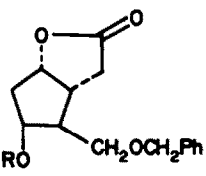
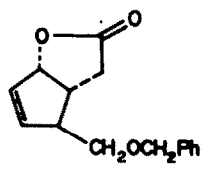
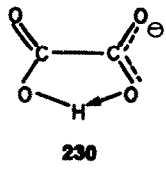


228 a: R = HCO
b: R = CH3CO

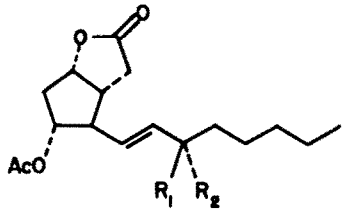


229



230

Inversion at C-15 was accomplished by Corey *et al.*[127] with superoxide ion. Thus potassium superoxide (KO_2) with a crown ether (18-crown 6) in a mixture of dimethylsulphoxide, dimethylformamide and dimethoxyethane effected conversion of the 15-mesylate of the 15R-prostaglandin intermediate **231a** to the corresponding 15S-isomer **231b** (75% yield after hydrolysis of the 11-acetoxyl).



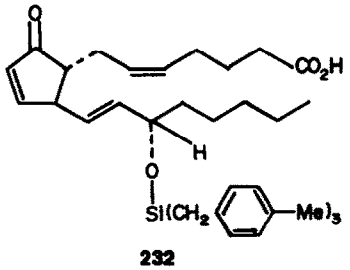
231

a: R_1 = OH, R_2 = H
b: R_1 = H, R_2 = OH

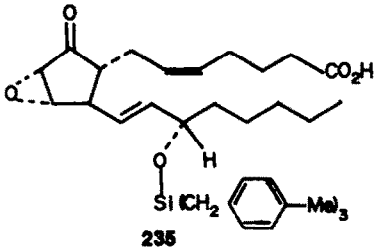
The usefulness of this new method in other areas was shown by effecting similar epimerisations of *trans*-4-*t*-butylcyclohexanol to *cis*-4-*t*-butylcyclohexanol and of cholesterol to 3-*epi*-cholesterol. This method has also been used to invert the hydroxylic centres at C_9 and C_{11}.[128]

(n) *Stereoselective formation of an epoxide using a controller group*

A stereoselective epoxidation of the 10,11-double bond was required by Corey and Ensley in connection with a method for synthesis of PGA_2 from PGE_2.[129] This was accomplished by attaching a controller group to the 15-hydroxy group which was so designed as to block the approach of the reagent to the β-face of C-11 in the cyclopentane ring. Using tri-*p*-xylylsilyl as the controller group in intermediate **232**, the 10,11-α-oxide **233** was formed by the action of alkaline hydrogen peroxide at $-40°$, with 94% stereoselectivity.



232



235

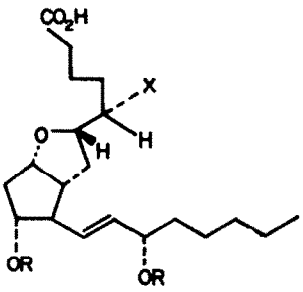
A molecular model of what appears to be the energetically favoured molecular conformation of **232** showed a strong shielding of the β-face of the cyclopentenoid unit by one of the benzenoid units in the controller group.

(o) *Construction of the unstable enol ether system of prostacyclin (PGI) under mild conditions*

Much recent chemistry in the prostanoid area has been directed towards the synthesis of prostacyclin (PGI_2) **235a** of which the structure was announced in 1976. Success in this work depended upon the discovery of suitable methods for generation of the chemically unstable enol ether system in which the double bond exocyclic to a tetrahydrofuran ring has the required *trans* stereochemistry.

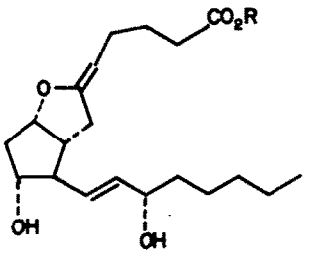
Several groups have succeeded in constructing prostacyclin from prostaglandin $F_{2\alpha}$. In the first synthesis, by Corey, Keck and Székely,[130,131] PGI_2, isolated as the methyl ester **235** (R = Me), was

obtained by elimination of hydrogen bromide, with potassium *t*-butoxide in *t*-butanol, from the bromoether **234a** (X = Br) of which THP ether **234b** was the major of the two products **234b** and **236b** from bromination with N-bromosuccinimide of the 11,15-bis THP ether of $PGF_{2\alpha}$. The *trans*-coplanar course of E_2 elimination from **234a** which must clearly be followed here, must produce the Z-geometry of the 5,6-double bond in **235** and hence the latter was obtained by an unambiguous and stereocontrolled route. The stereoisomeric bromoether **236a** (X = Br) was recovered unchanged after similar base treatment.



234

a: R = H
b: R = Thp



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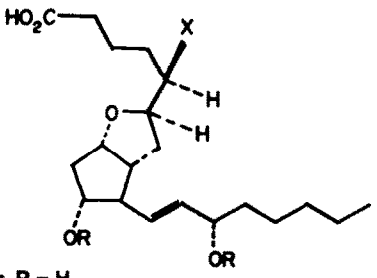
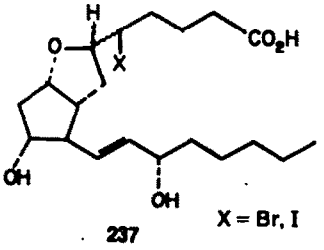


a: R = H
b: R = Thp **236**

Chinoin chemists[132,133] found that prolonged heating at 40–60°, with a base in an appropriate alcohol, of an isomeric mixture of haloethers **237** brought about dehydrohalogenation to prostacyclin of both isomers, thus rendering their separation unnecessary.

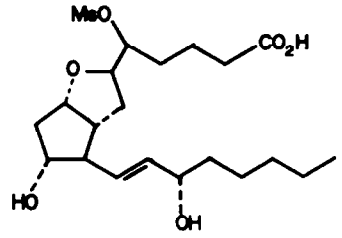


237 X = Br, I

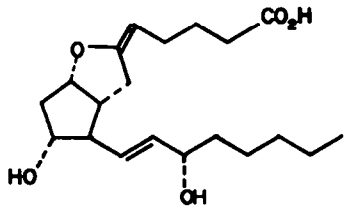
Whittaker[134] found that the methyl esters of **234a** and **236a** (X = I) were smoothly converted at room temperature into prostacyclin methyl ester **235** (R = Me) by 1,5-diazabicyclo-5-none (DBN) in the absence of solvent at room temperature and that reaction of these intermediates with methanolic sodium methoxide at room temperature, followed by treatment with 1N aqueous sodium hydroxide, afforded prostacyclin sodium salt (**235**, R = Na) in high yield.

Workers at the University of Pennsylvania and the Cardeza Foundation[135] cyclised the iodoether intermediates (methyl esters) with sodium ethoxide in ethanol and converted the resulting prostacyclin methyl ester to the sodium salt of prostacyclin by the addition of water. Upjohn Chemists[136] effected the haloether cyclisation with potassium superoxide in dimethylformamide containing a crown ether at 0–25°.

Interestingly the isomer of prostacyclin **239**, in which the 5,6-double bond is *cis*, was prepared by Corey, Székely and Shiner[137] by elimination with *t*-butoxide and *t*-butanol of the mesylate **238**, which had been prepared from the bromoether mixture **234a** and **236a** (X = Br) via treatment with potassium superoxide and a crown ether in dimethyl sulphoxide at 60°.

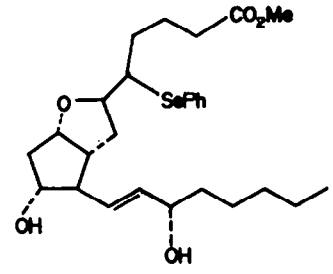


238

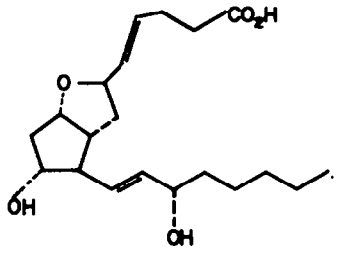


239

Nicolaou and Barnette[138] reported the synthesis of a prostacyclin isomer **241** by a novel ring closure induced by phenyl selenenyl chloride. $PGF_{2\alpha}$ methyl ester, on exposure to phenyl selenenyl chloride in methylene chloride at −78°, afforded the phenylselenoether **240** (mixture of diastereoisomers) as the major product, the regio- and stereoselectivity of the ring closure being expected on steric and proximity grounds. The prostacyclin **241** then followed from conversion of **240** to the selenoxide, *syn* elimination away from the oxygen to afford a *trans* double bond, and ester hydrolysis.



240



241

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